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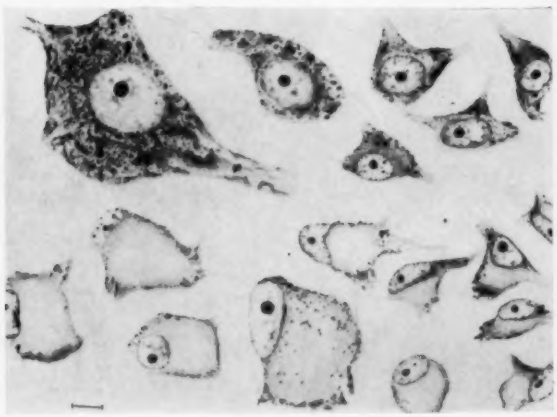

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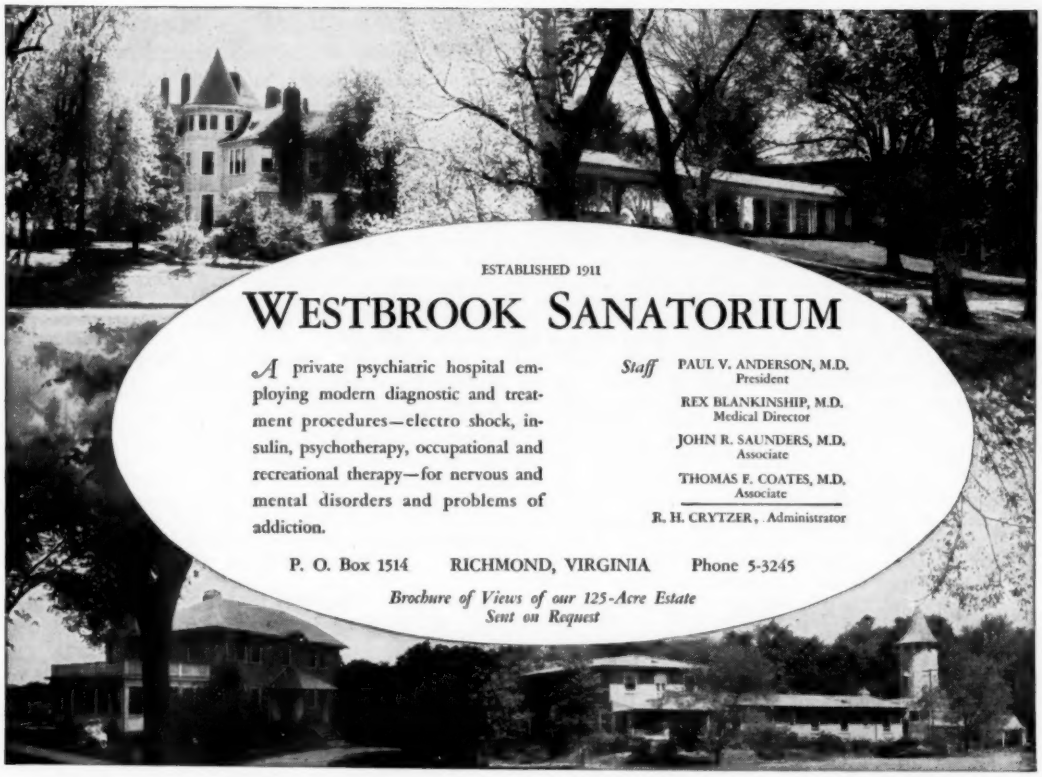
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Combined Chlorpromazine-Reserpine Therapy of Psychiatric Disorders

FREDERICK LEMERE, M.D., Seattle

The introduction of chlorpromazine and reserpine into the therapeutic armamentarium of the practicing physician has posed the problem of which drug to use in which type of nervous or mental disorder. The evaluation of the effectiveness of any treatment in psychiatric cases has always been difficult. This is made even more difficult when one is dealing with two drugs which are so similar in action and yet so consistent in their effect from one case to another.

It has been my experience that the same patient may not be able to tolerate one drug and yet respond nicely to the other. Much time is lost in trying to find out which drug is the more effective. As a consequence, an increasing number of patients are being started on combined chlorpromazine-reserpine therapy initially, with satisfactory results. The following study is an attempt to compare the results of chlorpromazine alone with reserpine alone and of each drug with the use of chlorpromazine and reserpine together.

METHOD

The 247 patients used in this study were private patients treated in a general psychiatric practice. They were approximately equally divided among schizophrenic, depressive, anxiety, and alcoholic reactions, with a smaller number of neurasthenic, obsessive-compulsive, and organic reactions. Eighty-four were tried on chlorpromazine alone, 75 on reserpine alone, and 88 on combined chlorpromazine and reserpine. Twenty-five of these patients were also given placebo capsules identical in appearance with the capsules used in part of this study.*

Results of Chlorpromazine-Reserpine Therapy in Psychiatric Disorders

Drug Used	No. of Patients	Drug Discontinued Owing to Side-Effects or Ineffectivity, Per Cent	Per Cent of Patients Helped
Chlorpromazine	84	51	49
Reserpine	75	54	46
Combined (chlorpromazine and reserpine)	88	34	66
Total	247	46	54

The dosage of chlorpromazine ranged from 10 to 400 mg. daily, and that of reserpine, from 0.1 to 4.0 mg. daily. The combination group received daily anywhere from 1 to 12 tablets or capsules containing 25 mg. of chlorpromazine plus 0.25 mg. of reserpine each. All of these patients were tried on medication for a minimum period of at least three weeks unless side-effects made continuation of treatment undesirable.

RESULTS

The results of this study can best be summarized in the accompanying Table.

Submitted for publication Feb. 14, 1955.

From the Department of Psychiatry, University of Washington School of Medicine.

* The Smith, Kline, and French Laboratories made available a generous supply of chlorpromazine (Thorazine), reserpine, and combined chlorpromazine and reserpine, all put up in identical capsule form, along with identical placebo capsules.

It will be seen from the Table that roughly one-half the patients treated were benefited. Chlorpromazine and reserpine were about equally effective, while the combined chlorpromazine-reserpine therapy was definitely more effective in relieving symptoms of nervous, emotional, or mental tension.

The reason for the better results from the combined medication was that larger doses could be given with fewer side-reactions. Apparently there is a synergistic effect when these two drugs are combined, while some of the side-reactions are canceled out. For example, chlorpromazine sometimes causes palpitation, while reserpine slows and regulates the pulse. Reserpine may cause nausea and diarrhea, while chlorpromazine counteracts nausea and may cause constipation. Chlorpromazine often makes the mouth dry, while reserpine may cause salivation.

There did not seem to be any advantage of one drug over the other in any of the different reaction types, except perhaps in the depressions. In a few patients, reserpine seemed to aggravate the depression, while no such effect was observed with chlorpromazine. Prolonged medication over a period of at least two or three months was sometimes necessary to get results in schizophrenia. The use of these two new drugs, and especially their combination, was unusually helpful in alcoholics because of freedom from addiction.

Of the 25 controls who thought they were getting chlorpromazine or reserpine or both but who were really getting placebo capsules, 15% said that they were helped, while 11% complained of specific side-effects against which they had been warned. This result emphasizes the strong suggestive effect of newer medications, especially those that have been given wide publicity in the press. It also suggests that it would be best not to warn patients too much regarding specific side-reactions from these two drugs, especially as few of these reactions seem to be dangerous.

I have found the following routine of medication to be the most satisfactory. Treatment is initiated with reserpine 1.0 mg. at bedtime and chlorpromazine 25 mg. t. i. d. This dosage is raised or lowered according to effectiveness and tolerance. After the patient is stabilized, it is often advantageous to prescribe 1.0 to 3.0 mg. of reserpine to be taken each night at bedtime for its prolonged and sustained calming effect, while chlorpromazine may be taken as necessary during the day, depending on the patient's level of nervous tension.

SUMMARY AND CONCLUSIONS

The combined use of chlorpromazine and reserpine is more uniformly effective in most psychiatric disorders than either drug alone.

There appears to be a synergistic action that gives maximum benefit, with minimum side-effects.

Therapeutic delay is minimized by initiating treatment with combined chlorpromazine and reserpine, rather than by experimenting first with one and then with the other drug to see which is more beneficial.

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Anxiety, Depression, and the Photically Driven Electroencephalogram

CHARLES SHAGASS, M.D., Montreal, Canada

Little is known about the neurophysiology of anxiety and depression, although these affective states are recognized as perhaps the most outstanding problems in psychopathology.* To advance research in this field, there is need for neurophysiological methods which will provide data bearing on the affective state of the intact human subject. The present study is concerned with the validity of one method which seems suitable for this purpose.

Several recent investigations have suggested that the effects of intermittent photic stimulation on the EEG may provide important neurophysiological correlates of emotional states. In most persons, certain flicker rates will elicit rhythmic EEG activity at the flicker frequency; this is called "photic driving." Walter and Walter [2] observed that photic driving varied with changes of mood in certain subjects. Ulett, Gleser, Winokur, and Lawler [3] carried out careful quantitative studies of photic driving in relation to anxiety. Employing automatic frequency analysis, they were able to demonstrate significant correlations between degree of clinically assessed anxiety proneness and some quantitative aspects of the driving response.

In a previous investigation,[4] I demonstrated that certain quantitative features of the photically activated EEG differentiated between anxiety and depression. Photic-driving responses to flash rates of 10 and 15 per second were compared in various groups of psychiatric patients and normal control subjects. The ratio between the EEG driving-response amplitudes at these two flicker rates seemed to provide the best index for differentiating anxiety and depression. A high 15:10 ratio, i. e., relatively greater driving at the faster rate, was characteristic of patients with anxiety states. Depressive patients, including both neurotic and psychotic types, had low ratios. The ratios of control subjects tended to fall in between those of anxiety and depression.

While these results indicated that the photic-driving response was related to affective state, it appeared that this correlation might not depend upon presence of psychiatric illness. Evidence to this effect was obtained from one control subject, who was tested on five separate occasions while experiencing different affective states. These tests showed that the driving response was labile, but that, in this subject, its fluctuations were correlated with affective state in the direction predicted from the differences observed among patient groups.

The purpose of the present investigation was to obtain further data bearing on the correlation between photic driving and affective state in single subjects. For this purpose, two subjects were studied over a period of several months. It was considered that the present longitudinal study might confirm and extend the previous, mainly cross-sectional, data concerning differentiation between anxiety and depression. A further aim was to determine whether the method could be used to assess the intensity of these affects.

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From the Allan Memorial Institute of Psychiatry, McGill University.

* Hoch and Zubin,[1] Foreword.

METHODS

Electroencephalograms were recorded with a Grass Model III-D instrument, using Bentonite paste leads. A Grass PS-1 photic stimulator, set at intensity 2, provided the light stimulation. The light was placed 4 to 5 in. from the eyes. The subject was asked to open and close the eyes before each stimulus sequence. Stimulation was started as the eyes were closed. Two stimulus sequences of 10 to 15 seconds' duration were carried out at each of the following flash rates: 6, 8, 10, 15 and 18 f. p. s. The order was always from the lower to the higher rates.

The subjects were two female laboratory technicians, well known to the investigator. Further details about each will be given together with results. Nearly all tests were done between 9:30 and 10 a. m. An attempt was made to do three tests weekly, but this was not always possible. Each subject kept a diary in which she recorded her feeling state on the morning of the test. No discussion of the diary entries took place during the course of the investigation. The subjects knew that the investigator was particularly interested in anxiety and depression, and they used these terms as they felt applicable. At the end of the investigation, the subjects were asked to write a brief autobiography, using case history form, and to define, as well as they could, the sense in which they had used terms descriptive of affect.

The method used for quantifying the photic-driving response is illustrated in Figure 1, which also shows three different quantitative patterns of response. The top record in Figure 1 shows good driving at 10 and poor driving at 15 f. p. s.; the middle record shows high-voltage driving at both frequencies, while the bottom record shows better driving at 15 than at 10 f. p. s. The arrows designate the consecutive 2-second strips, which contain the maximum-voltage driving response. These samples, containing maximum voltage, were measured by an additive ruler, which gives precise results.[5] The right parieto-occipital tracing was measured. For 10 and 15 f. p. s., samples from both stimulus sequences were measured and averaged. For 6, 8, and 18 f. p. s., samples were measured only for the second sequence at each frequency. Total amplitude for two seconds was converted to microvolts and divided by the number of flashes in the sample period to yield a mean amplitude. In Figure 1 the numbers under the samples represent the mean amplitudes at 15 and 10 f. p. s. In addition to the amplitudes, the ratio between them was determined.

RESULTS

Subject B.—This subject was 25 years old. She was married to a hospital intern. The health history was essentially negative, revealing only an appendectomy, frequent tonsillitis, and irregular menstruation. The superficial psychiatric history also contained little of a pathological nature. The subject reported that she had bitten her nails until age 4 and that in childhood she feared the dark, lightning, and cars; none of these phobias had persisted. She stated that at present she would become disturbed if someone held her down so that she was unable to move. She reported that when she became angry and could not express her feelings, she would continue to feel angry, and frequently lose her appetite. Anger against someone whom she did not know well was usually not expressed to that person, but she was able to express angry feelings to someone close to her.

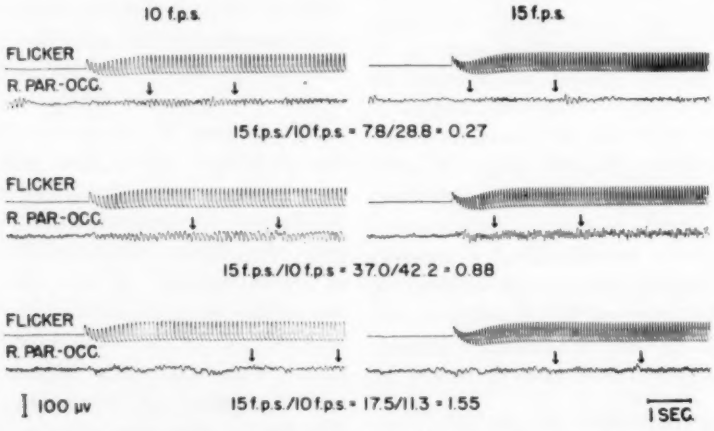

Fig. 1.—Photic driving at 10 and 15 f. p. s. in three tests. Upper tracing; photocell signal. Lower tracing; right parieto-occipital EEG. Arrows mark samples of maximal-driving response selected for measurement. Numerical values indicate mean number of microvolts per flash.

She described her use of the term "depression" as follows: "I feel sad, don't particularly want to talk to anyone. I prefer being alone, and frequently feel like crying. I get depressed premenstrually and occasionally when I am by myself for a long period of time." The feeling state which she designated as "anxiety" was described as follows: "When I am what I call anxious, I feel rather tense. I never feel as though something was going to happen, but not knowing what. I feel anxious when I have lots of work to do in a certain limited time, and occasionally in social situations where I don't know anyone." She occasionally

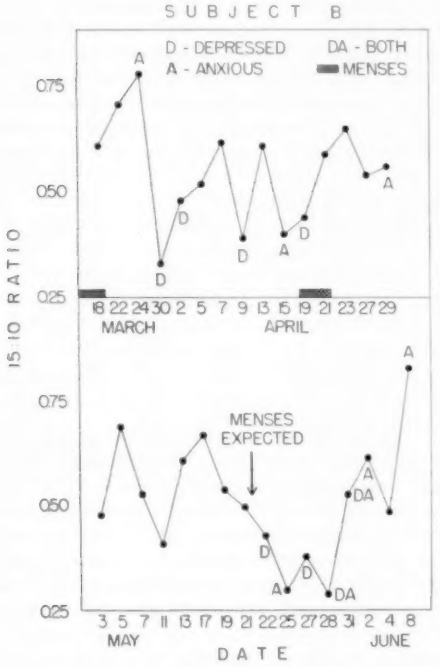

Fig. 2.—Serial 15:10 ratios for Subject B. Points not marked by *D* or *A* were obtained on test days when affect was reported as cheerful, relaxed, etc.

experienced what she described as "euphoria." "When I feel euphoric, I feel very happy, like to talk to everyone, do a tremendous amount of work."

Subject B had 31 tests over a period of 83 days. Her emotional state could be classified from her diary entries without any interpretations on the part of the investigator. In her own terms, there were three groups of affects, which could be labeled as depressed, anxious, and cheerful. In the diary, "anxious" and "depressed" were often qualified as "slight" or "moderate," but these qualifications were not considered in the data analysis. There were two days on which both the terms "anxious" and "depressed" were used; these states were classified as "depressed," since, for reasons discussed below, this was probably the dominant affect.

Figure 2 shows the 15:10 ratio for each test in relation to daily fluctuations in affect. It will be noted that on nearly all occasions when the subject stated that she was depressed, the 15:10 ratio was low. This finding would be anticipated from the results obtained with patient groups. No such consistent finding occurred when she used the term "anxious." However, it should be noted that, according to her own definition, she almost never experienced true anxiety. She used the term "anxiety" to describe a feeling of tenseness, usually related to a push of responsibility. The highest ratio found in the series of tests on Subject B was 0.83; this is close to the lower limit of ratios found in the anxiety patient group.

During the month of May, the subject experienced an unforeseen stress, which provided an unusual opportunity for experimental observation. Her menstrual period, which was expected about May 21, was delayed several weeks. This may have been associated with preparations to move to another city, the subject's husband having decided to take further training elsewhere. From May 22 to May 28 there were four consecutive test days on which a disturbed affect was reported and a low 15:10 ratio was recorded. The subject did not welcome an unplanned child, but was prepared to accept it if necessary. The entries in her diary during this time were as follows:

"May 21 (about the time the menses were expected): Feel so-so. Probably more cheerful than anything else. Not anxious or depressed.

"May 22: Feel rather depressed. My youngest brother's birthday is today, and I'm a little homesick. Not too much so, but a little. Slightly tired, as we got home late last night.

"May 25: Feel relaxed and a little tired. Haven't started menstrual period yet. Feel slightly anxious as to whether I'm pregnant or not.

"May 27: *Depressed.* I feel as I usually do before menstrual period. However, still think I may be pregnant.

"May 28: Mixed emotions. Depressed and anxious, but not much of either. Still wondering! However, I still feel as I usually do premenstrually.

"May 31: Feel so-so. A little depressed and a little anxious. Guess I'm pregnant, but would like to know for sure."

These entries suggest a depressed affect, expressed in a feeling of homesickness and reluctant acceptance of the situation. Two Ascheim-Zondek tests were carried out and were found negative. The subject began to menstruate on June 10, just before she left the city.

Graphs like the one in Figure 2 were drawn for responses at each flicker rate. None seemed to correlate as well with the affective state as the 15:10 ratio. The Table shows median responses at each flash rate for relaxed and disturbing days. The "disturbed" category included both "anxious" and "depressed" days; these were combined in order to provide adequate numbers for statistical comparison by the χ^2 test. This procedure was considered justified, since, in this subject, "anxious" seemed to lack specific meaning, other than awareness of some degree of tension. The responses to 15 f. p. s. and the 15:10 ratio were significantly lower on disturbed days than on relaxed days. These differences were due mainly to the consistent results obtained for "depressed" days. There were no other statistically significant differences.

The subject tested serially in the previous study [4] reported an euphoric mood the day following his engagement to be married. On that day the amplitude of his responses to 10 f. p. s. was twice that obtained on any of the other four days. Subject B reported an euphoric mood on two days; these results were included under the "relaxed" category. While her median driving amplitude at 10 f. p. s. for all tests was 19.3 μv, the amplitudes on the two "euphoric" days were 39.3 and 32.9 μv. Thus, in both subjects, euphoria was associated with unusually high-voltage driving at 10 f. p. s. Further data will be required to confirm this relationship.

Median Photic-Driving Response, in Microvolts

Subject	Affect (No. of Tests)	Flicker Rate (f. p. s.)					15:10 Ratio
		6	8	10	15	18	
B	Relaxed, etc. (17)	21.5	21.0	20.6	12.3	7.4	0.58
	Disturbed (14)	18.0	18.0	18.1	9.4	7.0	0.43
C	Anxiety not mentioned (9)	32.5	26.8	24.5	25.5	19.0	1.02
	Anxious (26)	30.7	24.0	23.2	27.0	20.0	1.15
	Very anxious (7)	33.3	21.8	19.8	29.8	15.0	1.45

SUBJECT C.—This subject was a 19-year-old, single girl. The health history was not contributory. There were a number of items in her personal history suggestive of a considerable degree of anxiety. The father, who had died about 10 years before, was remembered as one whom she feared greatly. She felt that he expected more of her than was humanly possible. She still anticipated inevitable criticism or disapproval from authority figures. The mother was described as rigid in her beliefs and ways. The subject bit her nails until the age of 15 or 16. She still had phobias in relation to flames and thunderstorms. She described herself as self-conscious and lacking in self-confidence, being extremely cautious about meeting new people and new situations. Most of the time she felt that she was unable to express herself verbally as well as she wished, and this she found very frustrating. She described herself as almost continually anxious, constantly experiencing a feeling of insecurity and an expectation of unjust criticism. "I need constant complimenting and continuous reassurance." As regards depression, she stated, "The only time I feel depressed is when I am physically quite ill." She denied ever experiencing euphoria.

The subject's statements about her almost constant anxiety and feelings of insecurity were in accord with observations by the investigator in the everyday work situation. It should be stated, however, that she functioned efficiently and reliably, even though under an emotional handicap.

A total of 42 tests were carried out on Subject C over a period of 116 days. The material provided by this subject's diary could be broken down only into a classification of varying degrees of anxiety, since she never reported being depressed and never felt comfortably relaxed. It was possible to do this without interpretation by the investigator and in the subject's own words. The 42 diary entries were subdivided into three categories. The first consisted of the nine entries on days when there was no mention of anxiety. On a few of these nine days the subject mentioned feeling fatigued, but on the whole these were the days when she felt least distressed. The second category contained 26 entries; on these days the subject described herself as feeling a little tense, or a little anxious, or just tense or anxious. The third category consisted of seven entries in which the subject described herself as feeling very tense or anxious.

The Table shows the median driving responses at the various frequencies for each of the three degrees of anxiety suggested by the classification of diary entries. There were trends for greater anxiety to be associated with higher-voltage driving at 15 f. p. s. and with lower-voltage driving at 10 f. p. s. These trends were of borderline statistical significance, as judged from determining critical ratios for differences in means. The results with 6, 8, and 18 f. p. s. were not statistically significant. Mean 15:10 ratios for the low-, intermediate-, and high-anxiety days, respectively, were 1.02, 1.17, and 1.45. Each of these means differed significantly from the others, indicating a significant relationship between the 15:10 ratio and the degree of anxiety.

This relationship is demonstrated in bar graph form in Figure 3.

Figure 4 shows the daily 15:10 ratios in relation to the degree of anxiety. Nearly all of the values are well into the range found in patients with anxiety states. A few items in this Figure are worthy of special note. On May 12, the subject showed the highest driving ratio of any of the 42 test days. The diary entry on that day read as follows: "I think I got up on the left side today. Did not sleep last night. It might be because of my exam tonight. However, all I know is that I feel lousy. Very tense, anxious, etc., etc. I've got every symptom in the book today. Irritable, upset. I've never felt this way." Thus, the very high ratio occurred in association with the highest degree of anxiety ever experienced by this subject.

On June 21, an attempt was made to give the subject sedation in order to see whether a drug-induced relief from anxiety would be accompanied by a change in the photic-driving response. Amobarbital (Amytal) sodium, 1 grain (65 mg.), was given on the first day, with very little effect. On the second and third days, the subject took amobarbital sodium, 1 grain, and methamphetamine hydrochloride, 2.5 mg. The effect of this combination of drugs on the first day it was taken was a sensation described as "euphoria." The subject did not care very much about what anybody thought, but, at the same time, she realized that this was due to the drug and did not feel that it was really herself. However, on the next day, the same dose of these drugs was associated with a feeling of rather severe anxiety, and the subject noted in her diary that she was more anxious than she cared to admit. She also stated that she had not felt well on arising that morning. The remaining tests during the investigation were taken under conditions of drug administration, but no combination of sedatives and excitants in small doses was able to produce either a feeling of relief from anxiety or any significant change in the photic-driving response. The day on which the subject described herself as "euphoric" did, however, yield the lowest 15:10 ratio of the entire series. This ratio, 0.85, was still above the highest one obtained with Subject B.

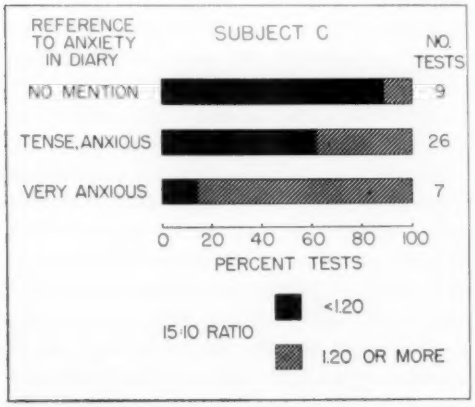

Fig. 3.—Relationship between degree of anxiety and 15:10 ratio in Subject C.

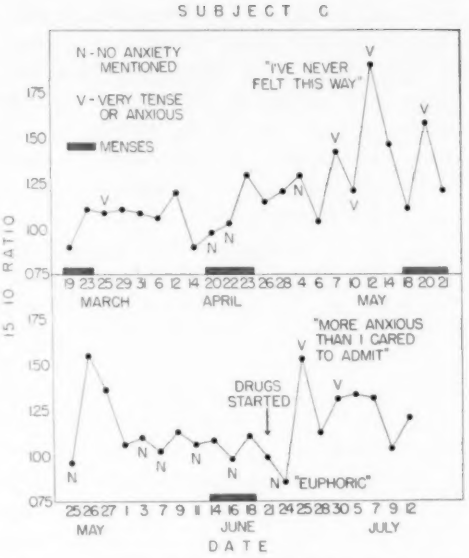

Fig. 4.—Serial 15:10 ratios in Subject C. Points not marked by *N* or *V* include all test days when anxiety or tension was reported, except those when the subject reported as being "very" anxious or tense.

Relation to Menstrual Cycle.—In the previous study,[4] the amplitude of photic driving was consistently higher in female than in male subjects. Since it was thought that this difference might be related to menstrual influences, amplitudes of photic driving at all frequencies were compared for the four quarters of the cycle in both subjects. No significant differences were found. In these subjects no correlation between phase of menstrual cycle and any measured aspect of photic-driving response could be demonstrated.

COMMENT

The findings of this longitudinal study of individual subjects confirmed predictions based on data obtained in the previous cross-sectional study of groups.[4] This concordance of results strengthens the evidence, provided by each investigation, in favor of the hypoth-

esis that anxiety and depression are characterized by quantitative differences in photic driving. Since these photic driving differences were similar in patient and in nonpatient subjects, the neurophysiological correlates of emotion, demonstrated in these studies, probably do not depend upon presence of psychiatric disease.

Present data suggest that the photic response may provide a valid objective indicator, not only of the kind of affect, but also of the intensity of a particular affect. There was a significant correlation between intensity of anxiety and the magnitude of the 15:10 ratio in Subject C. Subject B's lowest ratios were obtained during a period of objectively understandable emotional disturbance, associated with depressed affect.

The preliminary nature of studies so far carried out with this approach should be noted. Application of automatic frequency analysis and a wider range of stimulating frequencies should probably provide more definitive data. While practical application of the findings awaits further study, some uses suggest themselves. A very low 15:10 ratio in patients not suspected of being depressed may reflect a serious depressive disorder and should prompt further clinical inquiry. In one such instance of unsuspected depression the patient committed suicide immediately after leaving the EEG laboratory. The method may also provide an objective way of following affective changes during the course of therapy.

The superiority of the 15:10 ratio over responses to individual frequencies as a quantitative index of affective state is difficult to understand. One possible speculation is as follows: Suppose there were factors which influenced the amplitude of brain potentials and were unrelated to affective state. Uncontrolled variation of interelectrode distance could be one minor factor of this sort. Random variations, introduced by such factors, would reduce any correlation which might be observed between affective state and response to a particular flash rate. However, since the 15:10 ratio indicates relative response at two frequencies, irrelevant factors, affecting amplitude at the two frequencies equally, would have no effect on the ratio. Under such conditions, a correlation between affective state and frequency response might be better demonstrated by a ratio than by the response to individual flash rates.

There are a number of studies of psychiatric patients which might suggest associations between affect and resting EEG frequencies, similar to those found here for photic driving. Hurst, Mundy-Castle, and Beerstecher [6] have recently verified the claim of Davis [7] that, in manic-depressive patients, those with predominantly depressed phases have lower alpha frequencies than those with predominantly manic phases. Finley,[8] Heppenstall, Hill, and Slater [9] and Brazier, Finesinger, and Cobb [10] found greater than normal amounts of beta frequency activity in psychoneurotic patients, a large proportion of whom were presumably suffering from anxiety. However, Finley [8] found a higher incidence of fast activity in patients with depressive states than in psychoneurotic patients, and Hurst and associates [6] also found an abnormally high incidence of low-voltage fast records in patients with manic-depressive states. The available evidence thus indicates that excessive fast activity is associated with both anxiety and depression and does not support the idea that these affects may be differentiated by means of the resting EEG.

Ostow [11] found that subjects seem to drive best at or near the dominant frequency of their resting EEG. In my previous study,[4] no significant correlations were found between alpha frequency and amount of driving at 10 and 15 f. p. s. In that study, and in the present one, alpha frequency was not a significant indicator of anxiety or depression. Ulett and associates [3] also observed that many subjects without a fast resting EEG showed predominance of driving at fast flicker rates. Since they found some association between fast resting activity and anxiety proneness, they suggested that photic stimulation brought out a latent tendency toward rapid activity in anxiety-prone subjects. However, their investigation was not

concerned with depression or depression proneness.

Understanding of the mechanisms involved in photic driving is still limited. Brazier [12] recently provided a concise review, although for another purpose. One related concept, which seems important for present purposes, is that of "cortical excitability cycle." Lindsley [13] distinguished between recordable alpha rhythm and alpha activity, assuming that the latter is a basic cellular rhythm, associated with an excitability cycle in particular aggregates of cells. Gastaut and his collaborators [14] carried out an important study of "cortical excitability cycle" in men and animals. Their "cycle of excitability" was defined as all the modifications of excitability of a neuronal population following a preliminary excitation. Their method involved measuring the relative electrocortical responses to photic "conditioning" and "test" stimuli, presented at varying intervals. Chronological characteristics of the cycle were surprisingly similar in cat and man.

The excitability curves determined by Gastaut and associates provided three main variables, which, with the interpretation given them, were as follows: 1. Absolute and relative refractory periods. These together measure neuronal recovery time and could serve as a "time constant" of a neuronal system, characterizing the ability of the system to respond more or less quickly to repetitive stimulation. 2. Amplitude of the "conditioning curve." This reflects the strength of response of the system to a single stimulus, or degree of neuronal synchronization. 3. Amplitude of the "test curve." This expresses the postexcitatory state of subnormality or supernormality. The first and third variables would, obviously, be important determinants of the response to repetitive photic stimulation at a given rate.

Gastaut and associates studied the effect of various drugs on the excitability cycle. In relation to psychological problems, they described electrical signs associated with "calmness" and "nervousness"; these signs were based both on the cycle and on spontaneous rhythms. In their discussion, they placed considerable emphasis on the relations between the observed effects of barbiturates and amphetamines on the excitability cycle and the known behavioral effects of these agents. Barbiturates, which lengthen neuronal recovery time and reduce amplitude of response to the first and following photic stimuli, are used to relieve anxiety. Furthermore, it has been shown that tolerance to barbiturates may provide a quantitative estimate of degree of anxiety.[5] These facts would lead one to expect anxiety to be associated with relatively high-voltage driving at fast flicker rates. Amphetamine, which decreases neuronal recovery time, usually relieves depression and increases anxiety. The effects of amphetamine suggest that depression would be associated with less driving at fast rates and greater driving at slow rates.

From the foregoing statements, it seems that the present correlations between photic driving and affect agree with what one would anticipate from studies of cortical excitability cycle. This suggests that variations in photic driving and in affective state may both reflect fluctuations in cerebral excitability, the first at a measurable physiological level, and the second at a clinical level. More direct experimental studies of the interrelationships of excitability cycle, photic driving, and affect are needed to verify this formulation. Such experiments, which are feasible in at least some human subjects, should provide important information concerning the neurophysiology of affect.

SUMMARY

This investigation is a follow-up of a previous one, in which it was demonstrated that groups of patients with anxiety states and with depressions differed from one another and from nonpatient, control subjects in their quantitative EEG response to intermittent photic stimulation. In the present study, two nonpatient subjects were studied over a period of several months. The correlations between their photic-driving responses and their reported day-to-day fluctuations in feeling state were determined.

The results for these individual subjects, which showed significant relationships between affective state and photic driving, were in the direction predicted from the previous study of patient groups. Anxiety was associated with relatively greater driving at faster rates, while in depression driving was relatively greater at slower rates. Some evidence of a quantitative relationship between the response index and the intensity of a particular affect was also obtained.

It is concluded that the results support the hypothesis that anxiety and depression are characterized by quantitative differences in photic driving. These differences probably reflect a psychophysiological relationship, which does not depend upon presence of psychiatric illness. The interrelationships of photic driving, affective state, and "cortical excitability cycle" are considered.

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Brainwashing as a Factor in Psychiatric Illness

A Heuristic Approach

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The introduction of brainwashing into the armamentarium of propaganda methods is clearly fraught with social and political implications. However, primary in importance and causal in the sequence of these implications is the role of brainwashing in producing human behavior of a grossly aberrant or defensive type. This is because brainwashing is not merely a method of indoctrination but has as an integral component an extremely important determinant, that of forced behavior. Much has been written of this activity as a way of effecting the only mass desertion in the history of the U. S. armed forces, but little has been said of its significance in the possible future production of psychiatric syndromes in the thousands of returnees from Korean POW camps. This paper deals with a case of the latter. Rather than simply as a case study, it is presented primarily as a reconstruction of a method, "brainwashing"; an explanation of its results, and an attempt from their explanation to offer hypotheses which might be tested. This work must be considered only a heuristic approach; the data for the validation or refutation of these hypotheses are available in their entirety only to the medical services of the armed forces involved in the Korean conflict; consequently, one of the purposes of this paper is to stimulate the collection and presentation of these data.

In order to obtain the background for the understanding of the process of brainwashing, it is necessary to describe the activity in moderate detail. Essentially, it is the same as an attempt to obtain a truly global description of behavior in a primitive culture, an attempt which is possible only if the anthropologist describes the traditions, the motives, and the background of the culture, as well as the individual's actions. Ideally, a visit to the situation is desirable, but because of the nature of the setting in which brainwashing occurred, this was, of course, not possible. Consequently, it was necessary to interview several people who were incarcerated in Korean POW camps in order to describe adequately the modus operandi of brainwashing. The individual case is then described in the light of the material gleaned from these interviews. Further, in order better to understand the processes at work in brainwashing, it would seem necessary to view them within the frame of reference of the perpetrators of this activity, and therefore must be explained in terms of a background oriented, at least partially, toward the work of Pavlov.[1]

INTERVIEWS WITH FORMER PRISONERS OF WAR

The A. F. officer who was interviewed first was imprisoned in August, 1951. He was shot down over Korea, and immediately upon his being imprisoned, attempts were made to supply the Communistic viewpoint to him. He was given books by Gorky and Foster and copies of the *Shanghai News*, which were all written in English. The newspaper accounts showed gains by the Chinese Communist army. He was also given material, supposedly written by other allied POW's in the early part of the war, extolling the Chinese Communist treatment.

This officer has a B. A. degree in political science and had an interest in Communistic

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affairs in China after writing his senior thesis in college on the changes occurring in China. When the lectures expressing social and economic inequality in America were given, this officer was educated enough in political system and government to realize the obvious flaws in their presentations.

Besides the schoolroom approach of repetition of information by the same instructor, round-table seminars in the evening, and the offering of only Communistic literature or anti-American literature to read, the captors also offered minor favors of more tobacco or more sugar to those who showed a greater tendency to cooperate. The Lieutenant felt that perhaps there was confusion on the part of some enlisted men in interpreting the information that was given them and comparing it with what they knew the case to be, because either of lack of definite feelings or of information on political, social, and economic views.

On Thanksgiving of 1951, the POW's were asked to write a note of appreciation about the chicken and bread dinner they had received. Those who wrote good reports were rewarded by having them pasted with a red star and placed on a bulletin board.

Certain prisoners, he relates, had more intimate contact with the captors. There were peace committees composed of POW's whose job it was to talk to the new prisoners and attempt to get cooperation for peaceful behavior. These men were on separate rations. There was also a liaison officer who had to give the men the literature that the Chinese requested. In the camp, their loyalty was not questioned, as they were usually appointed and were generally not "progressives."

This officer at present clearly exhibits antipathy toward Communism. There are some factors worth noting, however—a large amount of information was given to the POW's, and most will use this information as their point of reference when thinking about Communism.

Another interviewee was U. S. A. F. 1st Lieut. K., who was captured by the North Korean Security Police on Aug. 11, 1951. He was not fed for three days, and was quite hungry and suffered from wounds. On the third day of his captivity, he was delivered to the Chinese, treated for his wounds, given something to eat, and given three copies of the *Shanghai News,* which told of gains by the Koreans.

He was moved shortly thereafter to another area and was once more given Communistic literature and was asked for comments. He pointed out it was usually the same fellow who brought the paper and asked the questions. On one occasion his food was taken away for four to five days and he was offered an opportunity to be fed if he would write an article on American aggression.

On another occasion, the captors asked that the prisoners write an article on how well they had been treated at Christmas time. The interviewee pointed out that usually the same prisoners would win these contests.

Lieut. K.'s way of handling the demands of his captors is well exemplified by his behavior during interrogation; he drew a false map, and because the material was actually known by the Chinese, he was punished by being forced to stand at attention for five hours in his shorts. Most of the time, however, Lieut. K. handled their demands by stating, "I don't know." On some occasions, he was caught in contradictions in his reports and was punished.

Classes were held for the prisoners, which included all officers and U. S. A. F. enlisted men who had been taken captive. Articles which had been written by Communists were taken up in these classes, and in the evenings the prisoners had to comment on these by means of a group discussion. Occasionally, these comments were rewarded by the Chinese group leader, saying that the person making the comment "had the right cognition." Generally, the people who received this praise were considered progressives.

Lieut. K. handled the situation as a captive by being nonconforming and by accepting some punishment. This punishment was tolerated adequately by him because it was

short-lived. There was no evidence of internal conflict in this man upon return.

The last interviewee is an Army Major. As a member of the Rangers, he had been conditioned to withstand physical punishment and hardship. He was captured on May 21, 1951, after eluding the enemy for several days in their own territory. After capture he was interrogated about military information. He gave none. After this questioning he was asked only personal social questions.

This officer explained that many of the prisoners felt that the Chinese were using the same methods of mass starvation for obtaining compliance as had been used on Chinese Nationalist soldiers. The prisoners were maintained on the barest minimum of sustenance, and, as a result, their numbers decreased from about 300 in July, 1951, to 200 by December, 1951. As this officer explained it, large groups of soldiers were placed in an orientation camp and given a starvation diet coupled with incessant Communist propaganda. The soldiers were not asked to accept it, but only to "listen with an open mind." If they became passive and nonhostile, their ration was increased and they were sent to a Learning School, where further indoctrination was presented.

In this camp the methods of schooling were continuous until the spring of 1952. The prisoners were subject to "forced formations," during which political or socioeconomic subjects were presented. The orientation was along lines extolling Communism and showing abuses in the American capitalistic system. There was no insistence that you listen to the lectures but attendance was mandatory, and anyone who fell asleep was made to stand at attention by the guard. During the lecture the same material was repeated over and over during the eduactional program.

This officer's first reaction to the interrogations and "brainwashings" was to be aggressive and hostile. After several occasions on which he was punished by beatings with a revolver and other methods, he assumed a more passive attitude in showing resistance, but his hate grew. He has had a long-standing acquaintance with Communist methods, as he was in Czechoslovakia after the end of World War II and witnessed Communistic procedure at work there. In the evenings at camp, when a round-table seminar or a "round table" was usually held by their Chinese political instructor, they would talk of home, baseball, and future plans. If asked to comment on a written article, they would usually paraphrase it so that their answer meant nothing. This officer always kept himself oriented as to what his country and its principles meant to him, and he, at present, shows an active and marked hatred toward Communism.

All of the interviewees have returned from a POW camp and have apparently successfully coped with "brainwashing." In the first two cases the intensity of the process seems to have been less than in the case of the Major, and less than reports of the "brainwashing" that was imposed on Army enlisted men, who were kept in a separate camp. Further, all of the interviewees started with a well-formed hostility toward Communism and handled the requests of their captors either through accepting short-lived punishment because of noncompliance or offering to the Chinese very ambiguous statements which could not be construed very strongly as agreement with Communist principles. Thus, it might be said that the conflict was directly between these POW's and their captors and was successfully resolved in the Korean camps. There was no conflict on their return to the United States.

CASE PRESENTATION

The following report is an outline of the case of a 25-year-old Army sergeant who was a Korean prisoner of war for 33 months, from Nov. 30, 1950, and who was released from camp on Aug. 24, 1953. He was returned to the United States on Sept. 9, 1953, and was processed in California along with other POW's. By the time his plane had arrived at Dallas, Texas, he was showing overt signs of his emotional disturbance. While eating in a restaurant at the air terminal, he felt that the people were staring at him and perhaps thinking that he was "progressive" because he had been a POW and had done something wrong. He then boarded the airplane again to continue on to Fort Jackson. The

crew members stated that he attempted to leave the plane at Shreveport, La., but he was returned. He did succeed, however, in Jackson, Miss., in going to the VA Hospital. There he complained that his "mind was messed up" and that his memory was gone. He could recall that he had been a prisoner for 33 months and that he was exchanged at Panmunjon on Aug. 24, 1953, remained in Korea several days, and then sailed to California by ship. He could recall some events that occurred on board, but not all events. He stated that he was unable to give many answers to the persons who questioned him on board ship because his mind was mixed up. He feared that the Army felt him to be a traitor because he was unable to answer the questions and that when he went home, the people would not want him and would disown him as a traitor. A routine physical examination and psychiatric evaluation were done, which revealed a psychotic state—type, undetermined. During the taking of a routine x-ray of the chest he felt that movies were being made of him. As a result, he became talkative and self-accusatory, stating that he wanted to confess.

He was transferred to an Air Force Neuropsychiatric Center near his home. The initial interviews revealed a tense patient who showed moderate blocking and ideas of reference, and had fears that the Army would court-martial him. He expressed no delusions or hallucinations at that time. He was confused over the way in which people would accept him after his prisoner status.

Past History.—The patient was born in a low-income farm community in Florida. He remained with the mother and father until the age of 4, at which time he went to live with his maternal grandmother because the father was unduly cruel to the boy. The home setting was one of a one-room log cabin, where two adults and two children lived. An uncle also lived there, to whom he felt close. He started school at the age of 6 and made average grades throughout, but was never very interested in school. Often, he felt different from the other children because he did not have the proper clothes to wear. In the ninth grade, he quit school and started to work. He drove a truck for a canning plant for approximately two years prior to coming into the service. He enlisted in the service in 1949 and, after basic training, was sent to Korea in August, 1950. As soon as he arrived, he was sent to the front lines. His position in the squad was that of a Browning automatic rifle man. Later, he became the jeep driver for the company commander. The patient stated that while overseas, when on guard duty one evening, he had an experience which was similar to that one he had just prior to coming into the hospital. While in the fox-hole, he heard someone approach and asked for the password. It was given, and since it was dark he could not see who it was. He grabbed his rifle and started at the figure with his bayonet. For several minutes he felt he did not know what he was doing. The approaching figure was the company commander, and he called the patient by name, and it was only after a lapse of time that the soldier was able to realize whom he was attacking. On Nov. 30, 1950, his company was surrounded, and he was captured by the Koreans. He was shot superficially in the leg and at that time crawled into the back of a trailer, hoping that the enemy would not find him. When he was uncovered, he feared that the enemy would cut his throat, which he thought to be the usual treatment of those soldiers who were captured. He was placed in a POW camp, and in the first months of his imprisonment he had several episodes of diarrhea and was always maintained on a minimum diet. In the encampment, forced formations were ordered, and this soldier, along with the other prisoners, attended repeated lectures in which a political instructor would lecture in English on Communistic or anti-American subjects. The patient stated that he often heard lectures on the same subject until he began dreaming about them. This patient was picked by the Chinese to be a "group monitor." His duties consisted of passing out pamphlets for the men to read which pertained to Communistic doctrine. He stated he never believed the material, and that the men did not resent his passing these out, because someone had to do it. He felt that if he did not do this particular work, someone else would. Later, he was again picked for special schooling and a series of more intensive lectures. One of his main concerns during his imprisonment was that the men would think that he was a Communist. He stated that the Chinese asked him to watch the men and report on their actions, but that he never did. He did not directly refuse to carry out this request but just never reported anything. He felt that he was never considered a "pro," because he repeatedly asked the other men for reassurance that they did not consider him to be one. Prior to being in prison, this soldier had practically no information on political systems or government. As a result of his long incarceration, he now has significant information on Communism which has been presented to him by Communists. While in the camp, the prisoners were on occasions asked to write down their impressions or statements about pro-Communistic themes. Some of the topics concerned prisoner treatment and the sanitation programs established in the POW camps and the general benefits of Communism. There was a method of reward for those compositions with more suitable wording in that they were pasted on a bulletin board for all to read.

Often during his imprisonment, this soldier, who had no formal education or specific interests in politics or socioeconomic developments, became confused when topics of racial segregation, poverty in

a country with a high standard of living, and other controversial topics were presented.

The exact role he was playing while a prisoner did not seem to have traumatic significance to him while in the camp, but minor episodes bothered him more severely when he did return to the States. Certainly, as more and more was seen of him in the hospital, it became evident that he had absorbed some of the ideas offered to him in the POW camp.

COMMENT

The reconstruction of the essential elements of the brainwashing to which the patient was subjected requires some knowledge of the research done by Pavlov and others of the experimentalists who worked in the same field. Particularly important was the discovery in Pavlov's laboratory of the experimental neurosis.[1] In working with dogs, it was found that when a difficult differentiation was utilized, namely, an almost impossible differentiation between a true circle, which was always accompanied by feeding, and an ellipse, the axes of which made it approximate a circle closely but which was never accompanied by feeding, the animal, not able to determine, because of the perceptual difficulty, which stimulus would be rewarding and which would not be rewarding, became excited and struggled and howled, in contradistinction to its former quiet behavior when two *easily* differentiable geometrical patterns of an ellipse and a circle were used. This observation was extremely important as an indication that an experimentally induced conflict could produce a disorder not unlike those seen in psychiatric patients. Confirmation of these researches has been made by other workers, particularly Gantt.[2]

Consideration must also be given to the work of Maier, who, also working with animals, found that a frustrating situation, producing a conflict which was unresolvable, was instrumental in the formation of what he considered non-goal-directed behavior and which had among its components aimless running and catalepsy with waxy flexibility.[3] As to whether this aberrant behavior is a defense against the anxiety engendered by the conflict or a chaotic result of the conflict is a theoretical matter which is of no great moment at this point in this formulation.[4]

In a perspicacious article recently, Meerloo makes reference to the fact that speech is considered by the Pavlovian group to be a conditional reflex function of the human brain.[5] In the paper presented here, it is offered that there are three types of conditional responses, that is, that behavior is the sum total of verbal, thinking, and motor activity. Recognition is also made of the work of the more sophisticated learning theorists that much, if not all, behavior is learned by reinforcement, i. e., by drive reduction which might occur by relief from physical punishment, or by relief from the fear inherent in this, or by a positive reward, which, in turn, would cause the assuagement of basic or learned needs.[6]

In light of these concepts, it becomes possible to reconstruct the situation in which the patient referred to above was involved. The patient in the course of brainwashing was forced into singing Communist songs and writing pro-Communist statements. Although at first he probably did not accept these, he was rewarded for these activities, and consequently the behavior must be considered as having been reinforced. The role of a high-drive state as a result of hunger and the assuagement of the hunger as a reward must be taken into account. Further, he was given tasks to accomplish by his captors and received various types of gratification for these activities. If, in the beginning, the patient did not believe in his statements and activities, there would have inevitably been an internal conflict between his motor and speech responses as opposed to his thinking. Only three ways were available in which to resolve this conflict. The patient might have been able to outwit his captors, as some of the interviewees were able to do, or he could have refused to do their bidding, which would have resulted in punishment and no rewards. Either of these two ways of handling the situation would have resulted in a resolution of the conflict. Either of these methods would have provided a short-lived conflict with authority, which would, judging from the

interviews with the POW's who successfully handled the brainwashing, have abated in time. Or the patient could have started to resolve the conflict by thinking in favor of his captors, and, from the clinical material, this is what he finally did. The proof for this was his being sent to a camp for more intensive indoctrination, a thing which probably would not have happened had he not been viewed by the captors as brainwashed, at least in part.

After the patient was repatriated, he met with another problem. In this case, the conflict which arose was between his thinking and the society to which he was returning. As he returned to the United States, he met with more and more hostile attitudes and people who concerned themselves with attacking as traitors those who had suffered from brainwashing. This inescapable conflict produced in the patient the symptoms of confusion and fugue state.

The major task in the psychotherapy of this patient is to extinguish the acute anxiety and other symptoms made manifest by the conflict. This was done by the psychotherapist's not responding to the patient in a hostile manner and by allowing the society in which the patient had been reintroduced to provide its own and gradual system of reinforcements—first for verbal and motor behavior and then by allowing thought to change in order to avoid internal conflict. The reason that inescapable conflict did not occur on his first being brainwashed, i. e., conflict between induced thought and thought already present, is that in the case of the patient there was no strong politically pertinent feeling of any sort present before the brainwashing.

The construction of the above framework makes it possible to hypothesize two suppositions, the latter of which is certainly capable of being proved. First, it is possible to say that the choice of not being repatriated, which choice several men took, was behavior which could be considered defensive and protected these men against conflict. Secondly, because of the intensity of the conflict, it is possible to postulate that among the Korean returnees, there would be more mental illness than in a comparable group from the general population or from the German and Japanese POW camps of World War II, keeping constant, of course, the time factor in all three groups, utilizing the period of the length of time from repatriation in the Korean camps to the time of the survey.

SUMMARY

A case is presented in which the patient was a very disturbed young man who was incarcerated in a Korean POW camp and who was subjected to rather intensive brainwashing. Three other, but healthy, POW's were interviewed in order better to understand the technique of brainwashing and the general settings in which the patient lived. An explanation of the sequences of events which followed repatriation of the patient is given, and a theory is evolved to explain why several prisoners refused to return to the United States. Further, the explanation is utilized to make a prediction concerning aberrant behavior in the mass of returnees.

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Variations in the Plasma Fibrinogen During the Course of Multiple Sclerosis

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The purpose of this work is to assess the values of the plasma fibrinogen found during the course of multiple sclerosis.

On the basis of pathological-anatomical and experimental investigations, Putnam * was the first to advance the theory that in the case of multiple sclerosis thrombi are formed in the small veins of the central nervous system and consequently cause the formation of the characteristic plaques.

Broman [4] and Haarr,† on the basis of pathological-anatomical investigations, defined multiple sclerosis as a periphlebitis; however, they were unable to demonstrate coagulation thrombi in plaques in patients with the disease. Through his investigations, Fog [5] found that in this disease the plaques of the spinal cord occur in relation to the veins. It is often difficult to distinguish between the acute signs of this disease and those of vascular attacks; moreover, external factors which increase the coagulability of the blood seem to aggravate multiple sclerosis. Furthermore, it has been shown that the mechanism of coagulation in multiple sclerosis is abnormally labile.[6]

Although it has proved impossible to demonstrate coagulation thrombi in plaques in multiple sclerosis, attention must be drawn to the fact that in human pathology thrombi cannot be identified with coagulation thrombi, because the blood platelets are able to agglutinate alone and so block the vessels.‡ As mentioned, several facts in connection with multiple sclerosis indicate that the characteristic plaques are produced by an agglutination of the thrombocytes and the ensuing blockage of the vessels. In this connection it appears to be of importance to find out whether in this disease factors are demonstrable which facilitate the agglutination of thrombocytes. If, for instance, the plasma content of proteins having a small electric charge, i. e., fibrinogen and globulin, is raised, the electric charge of the thrombocytes is reduced, as is shown through increased agglutinability.[10]

Little information is available as to the plasma fibrinogen content in multiple sclerosis. Putnam § states that in this disease the amount of plasma fibrinogen is sometimes above normal. On the other hand, Huszak and Szák [13] were unable to demonstrate any essential change in the content of plasma fibrinogen as compared with the normal.

In order to assess how much importance can be given to a rise in the content of plasma fibrinogen, it is of value to compare the plasma fibrinogen content with the sedimentation rate, as it has been demonstrated || that an increased fibrinogen content and a rise in the sedimentation rate will usually occur simultaneously, and this should have

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‡ References 7 to 9.

§ References 11 and 12.

|| References 14 through 17.

a direct causality. However, others,¶ who also found that the sedimentation rate rose when the values of plasma fibrinogen increased, did not feel convinced of a causal connection.

Later investigations # have shown, however, that the sedimentation rate is dependent on several factors, the process being a complicated one. It is not only the fibrinogen which is of importance, but also the other serum proteins and the relationship of the values for these proteins, as well as the hemoglobin concentration, the erythrocyte count, the serum lipoids, and the temperature.

In a group of patients suffering from multiple sclerosis, a correlation coefficient for the fibrinogen content and the sedimentation rate was found to be of similar value to that for normal persons.[23] Moreover, on the whole, a relatively high content of plasma fibrinogen has been found also [23] as compared with the sedimentation rate, but no previous attempts have been made to show whether variations of the fibrinogen content occur during the course of the disease.

EXPERIMENTAL TECHNIQUE AND CLINICAL MATERIAL

The sedimentation rates were estimated according to the technique of Westergren,[24] and the plasma fibrinogen, according to the method of Gram.[16] In order to exclude a suggestive influence on the objective investigations, the experimental results were not gathered together until after the termination of the periods of observation. The values found are shown in the curve.

The investigations comprised 16 patients with multiple sclerosis, whose case histories will be stated briefly below. The clinical material available for the investigations was so composed that in one patient only was the course of the disease rather acute, whereas in the others it was protracted. Neurological examination of the patients was carried out on the average every fortnight, with the exception of the acute case, where examinations were more frequent. Moreover, the courses of the disease are shown on the charts, which are designed so that within each date column the patient must be visualized as facing the examiner, the left half of the date column representing the patient's right, and the right half, the patient's left. The numbers indicate how high the limbs could be lifted. Descending hatching, or arrows pointing left to right, indicate an improvement of the condition, and the opposite, deterioration. The patients were periodically given physical therapy and vitamin B, without this therapy having any apparent influence on the occurrence of the attacks.

REPORT OF CASES

CASE 1.—A woman aged 54. The disease started when she was 29 years old, with paresthesiae in both feet. In the early course there had been considerable, long-lasting remissions, but during the last 10 years the condition had been stationary, with only minor changes. At the time when this investigation was begun the patient appeared to be mentally normal. There was a weak nystagmus on looking to the right. Ophthalmoscopy revealed no definite optic atrophy. There was increased tonus in both arms, and the reflexes were brisk, especially on the right. The power was diffusely reduced, mostly on the left. The finger-to-nose test showed some ataxia. The abdominal skin reflexes were absent. The power of the lower limbs was slightly reduced. There was a considerable increase of tonus on both sides, with brisk reflexes and a bilateral Babinski sign and ankle clonus. The heel-to-knee test showed some ataxia. The gait was spastic and slow, and walking was possible only with the support of one helper.

CASE 2.—A woman aged 55. At 31 years of age the patient developed paresthesiae in both feet and a feeling of insecurity on walking. During the course of the disease there had been protracted remissions, but the condition gradually became much worse. The patient was normal mentally. Nystagmus could not be demonstrated. Ophthalmoscopy showed the presence of optic atrophy. There was increased spasticity of tone in the left arm, and the power was diffusely reduced on both sides. The deep reflexes were brisk in the right arm and weak in the left. There was ataxia on the right side. The abdominal skin reflexes were absent. There was paralysis of the lower limbs. There was increased spasticity, with equal, exaggerated deep reflexes, bilateral ankle clonus, and the Babinski sign. The patient was unable to raise her legs and could not walk.

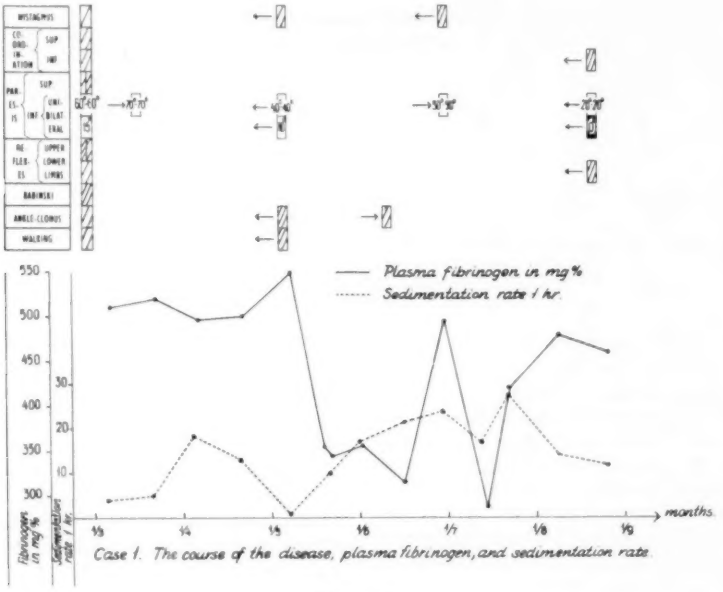
CASE 3.—A woman aged 38. The patient fell ill at 28 years of age. The first symptom was difficulty in walking. The condition deteriorated through the years, the course being interrupted only by partial remissions. The patient was par-

¶ References 18 through 20.

References 21 and 22.

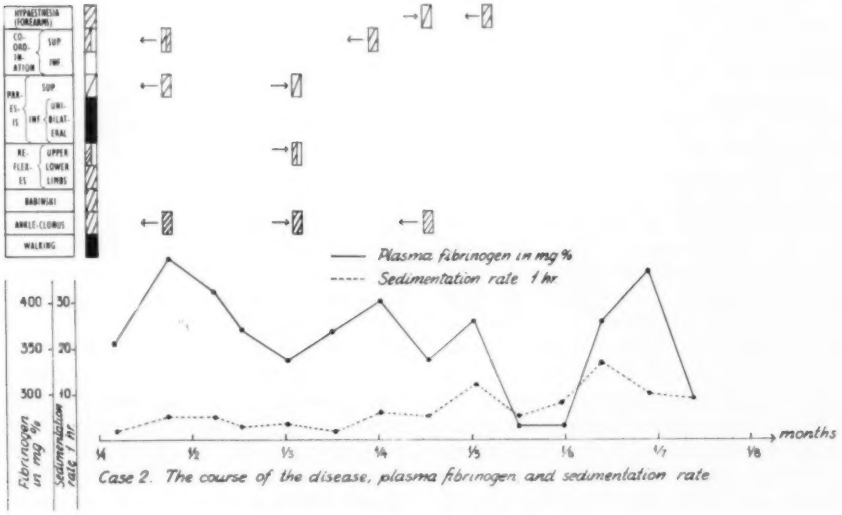
tially demented. There was gross nystagmus. Nothing abnormal was shown on ophthalmoscopy. Power was good in both arms. Tonus was slightly increased, and the deep reflexes were brisk, especially on the right side. The finger-to-nose test showed ataxia on the right side. The abdominal skin reflexes were absent. The power was diffusely reduced in the lower limbs. There was spasticity. The reflexes were brisk, especially on the right side, and could be elicited over a wider zone. Moreover, ankle clonus and the Babinski sign were present bilaterally. The patient could not lift her legs together with her knees straight. The gait was very spastic, and she could walk only when she was supported by two helpers.

CASE 4.—A woman aged 43. The first symptoms of the disease occurred when the patient was 24 years old, presenting as weakness in the lower



Case 1. The course of the disease, plasma fibrinogen, and sedimentation rate.

Figure 1



Case 2. The course of the disease, plasma fibrinogen and sedimentation rate

Figure 2

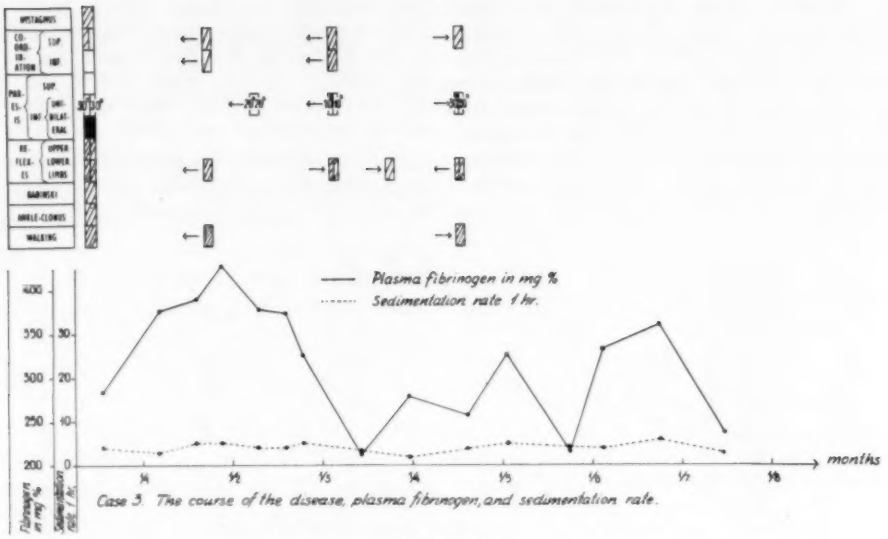


Figure 3

limbs. Since then there has been continuous deterioration, although in the beginning it was broken by almost complete remissions. However, gradually the remissions became incomplete, and in recent years there have been only minor changes. At the start of the investigation the patient was normal mentally. There was moderate nystagmus at the extreme positions of the eyes. Nothing abnormal was seen on ophthalmoscopy. There was slight hypertonia and slight decrease of power in the right upper limb; in addition, the deep reflexes were weaker on the right than on the left. Apart from that, nothing abnormal was found in the upper limbs. The abdominal skin reflexes could not be elicited. There was reduced power in both lower limbs and marked spasticity. Deep reflexes were brisk and equal on the two sides. There was a bilateral ankle clonus and Babinski sign. The patient could not raise her legs, and could not walk, even with support.

Case 5.—A woman aged 36. The illness started when the patient was 24 years old, with headache, gyratory dizziness, and unreliable memory, and with dim vision in the right eye. The condition remained equivocal through the years, with partial remissions. On examination the patient was found euphoric and demented. There was a brisk, undulating nystagmus. Ophthalmoscopic examination showed bilateral temporal optic atrophy. The neurological aspects of the upper limbs were normal. The abdominal skin reflexes were absent. There was spastic increase of tone in the lower limbs. The deep reflexes were brisk, especially on the left side, where they could be elicited over a wider zone. There was ankle clonus, especially on the left side, and a bilateral Babinski sign. The right lower limb could be lifted 10 degrees in extension, although with reduced power. The left one could not be raised. The heel-to-knee test showed ataxia. The patient was unable to walk.

Case 6.—A woman aged 22. She fell ill at the age of 19, the initial signs being left-sided retrobulbar neuritis and paresthesiae in the right hand. The course of the disease had been intermittent, but there had not at any time been a complete remission. On examination slight nystagmus at the extreme positions of the eyes was found. Ophthalmoscopy showed bilateral optic atrophy. The upper limbs were normal, apart from slight intention tremor and slight asynergia on the left side. The abdominal skin reflexes were absent. The lower limbs showed a spastic increase of tonus; brisk reflexes, demonstrable over a wider zone; bilateral brisk ankle clonus and a tendency toward patellar clonus, and a bilateral Babinski sign. There was slight paresis of the right lower limb, which could be raised 45 degrees with extended knee; the left leg could be raised 90 degrees. The legs could not be raised together. The heel-to-knee test showed some ataxia. The gait was slow and very spastic. As shown on the curve, the patient was treated with cortisone (25 mg. four times daily) for a period and for a later period with corticotropin (10 mg. four times daily); but it was not possible to demonstrate any improvement objectively, and, in addition, the patient felt worse. At the start of the illness, however, the patient had reacted favorably to this treatment. In August, 1952, the patient developed pneumonia, which was treated with procaine G penicillin.

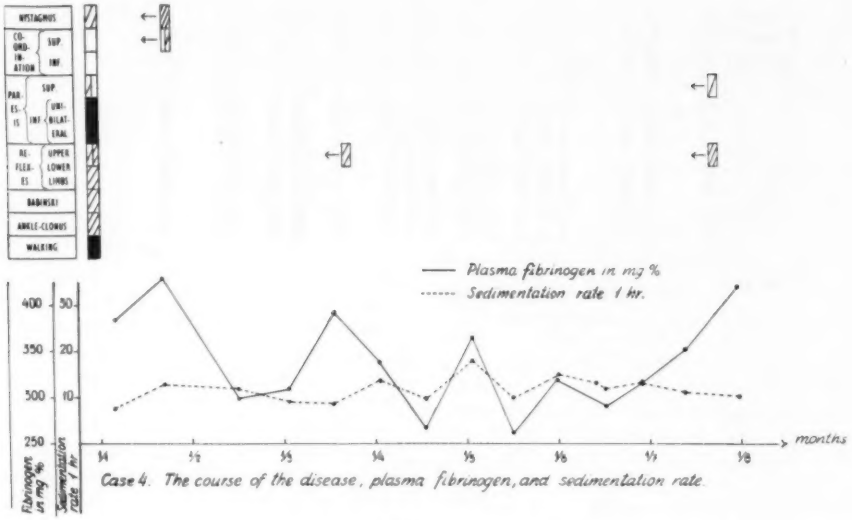


Figure 4

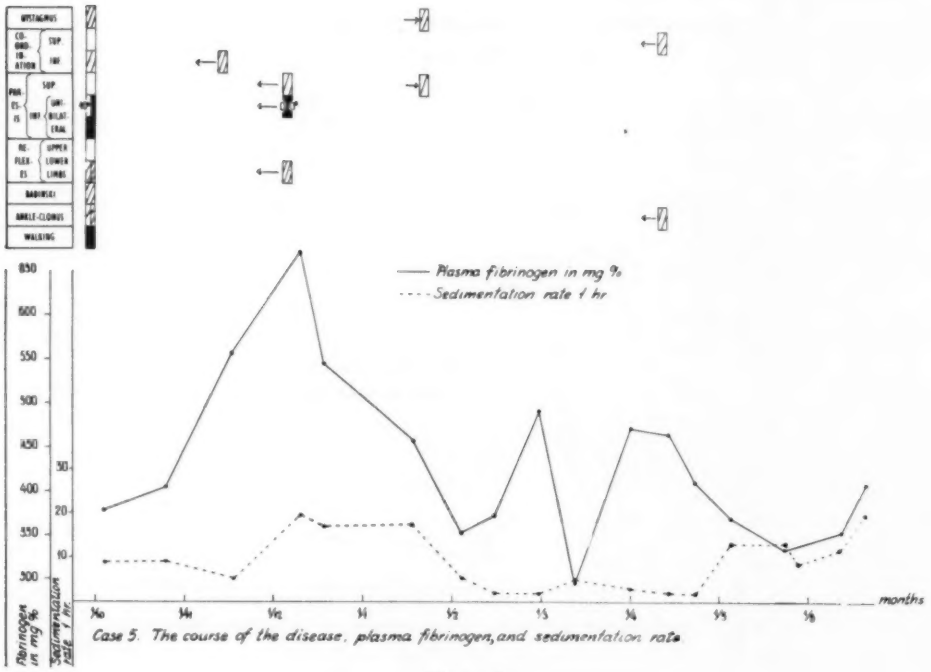
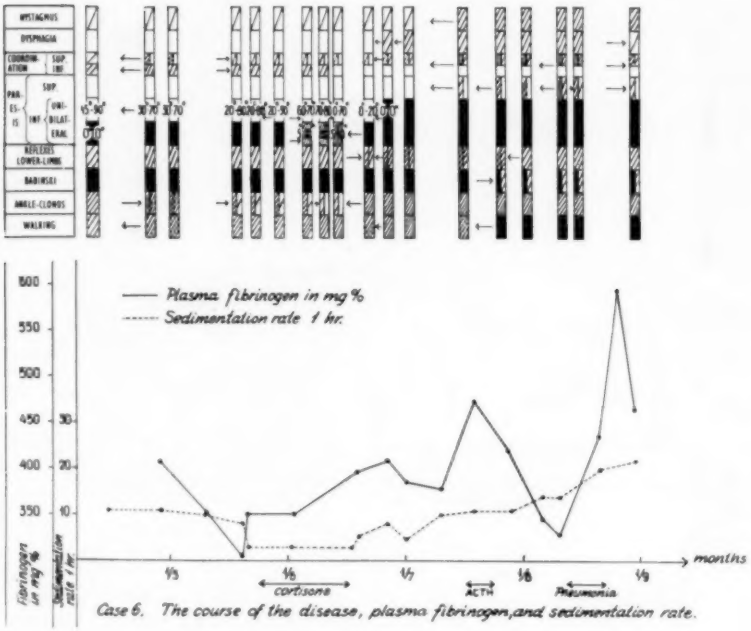


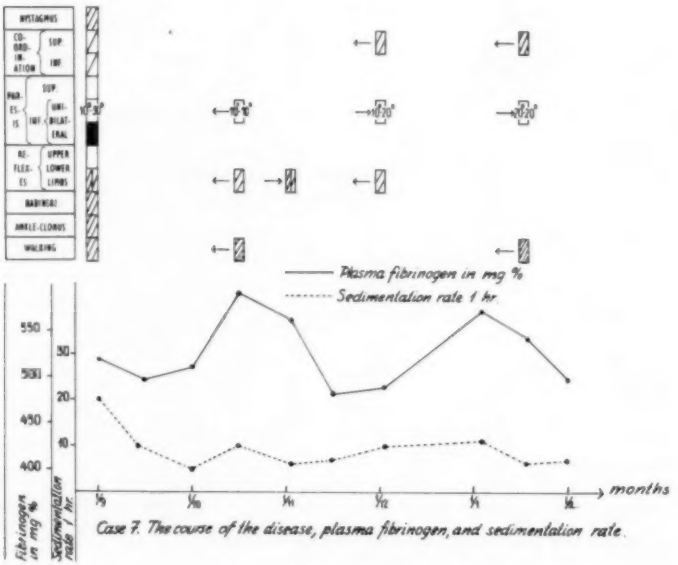
Figure 5

CASE 7.—A woman aged 46. Three years previously she developed a feeling of uncertainty in the lower limbs and experienced some dizziness. During the following year the condition remained relatively stationary, but in the last few months before admission to the hospital there was increasing difficulty in walking. The patient was somewhat euphoric. The speech was staccato. When the patient looked to the left, paresis was demonstrated and nystagmus was present. Ophthalmoscopy showed the presence of temporal optic atrophy. There was slight final uncertainty in the



Case 6. The course of the disease, plasma fibrinogen, and sedimentation rate.

Figure 6



Case 7. The course of the disease, plasma fibrinogen, and sedimentation rate.

Figure 7

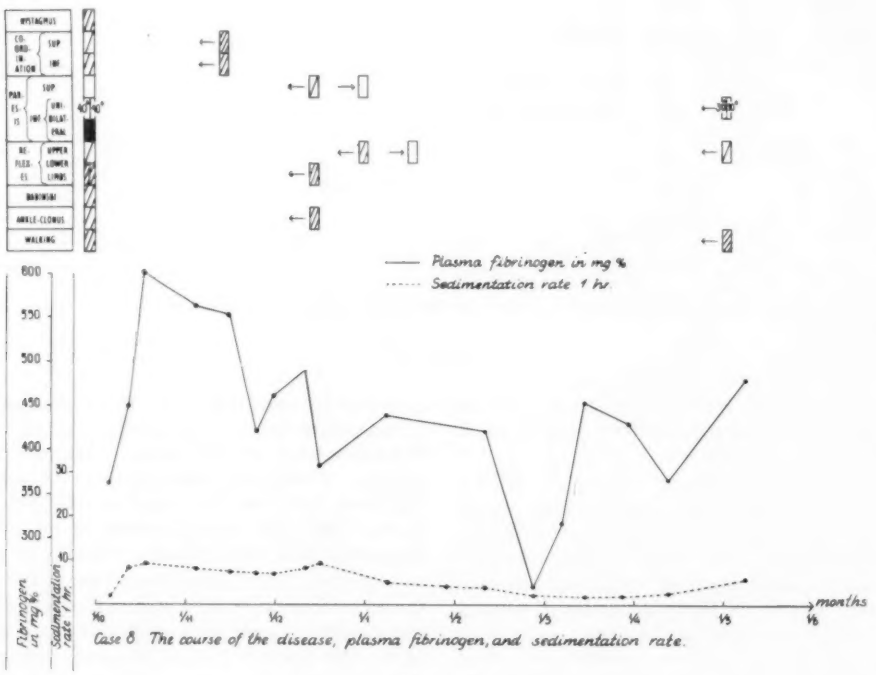
finger-to-nose test and slight dysdiadokokinesia. The abdominal skin reflexes were absent. There was a spastic increase of tone in the lower limbs, and power was diffusely reduced, especially on the right side. The knee jerks were brisk, especially on the right. There was a bilateral ankle clonus and Babinski sign. The heel-to-knee test was performed with terminal uncertainty. The patient could walk with the help of one person.

CASE 8.—A man aged 39. The patient became ill at the age of 24. The disease presented with difficulty in walking; he had special difficulty in

controlling his left leg. The course of disease had been one of steady progression, with no marked remissions. At the time when the examinations began, the patient showed some mental depression. There was marked horizonal nystagmus. Ophthalmoscopy showed left-sided temporal optic atrophy. The deep reflexes in the upper limbs were moderately brisk and equal on the two sides. There was slight past pointing in the finger-to-nose test, and gross terminal tremor. The power was normal. The abdominal skin reflexes were equal and moderately brisk. The right leg showed slight spastic increase of tone. The deep reflexes were hyperactive, especially on the right, and were demonstrable over a widened zone. There was bilateral ankle clonus and a bilateral Babinski sign. The heel-to-knee test showed ataxia. Each lower limb could be raised alone through 40 degress with extended knee, with fairly good power, whereas the legs could not be raised together. The patient was unable to stand or walk unless aided by one person.

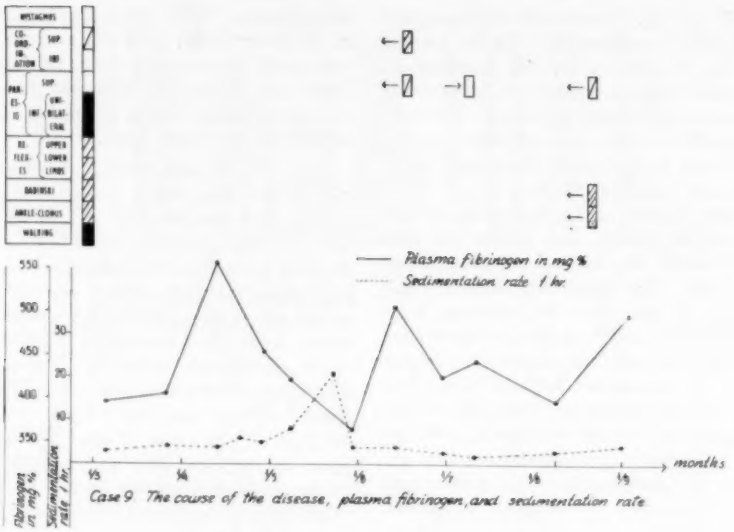
CASE 9.—A man aged 43. Since the age of 15 he had suffered from steadily increasing difficulty in walking, relieved by brief remissions. Mentally, the patient was subintelligent and demented. Ophthalmoscopy showed bilateral temporal optic atrophy. In the upper limbs the reflexes were brisk and equal, and there was some uncertainty in the finger-to-nose test. The abdominal skin reflexes were present. There was a spastic increase of tone in the lower limbs. The reflexes were very brisk and were demonstrable over an increased area. There was bilateral patellar and ankle clonus and a bilateral Babinski sign. No active movement was possible in the lower limbs.

CASE 10.—A man aged 51. When the patient reached 35 years of age, he developed difficulty in walking and had difficulty in keeping his balance. The condition remained relatively stationary for the first five years, after which there were fluctuating remissions, each lasting several months; but on the whole the condition has worsened with the years. Objective examination showed the patient to be somewhat euphoric. There was slight nystagmus. Ophthalmoscopy showed nothing abnormal. There was slight right-sided increase in the tone of the upper limbs. The reflexes were equal on the two sides and somewhat increased. In the finger-to-nose test on the right there was relatively gross intention tremor and past pointing to the left. The abdominal skin reflexes were absent. In the lower limbs there was a marked increase of tone, and movement was accompanied by very considerable tremor. The reflexes were brisk, equal, and demonstrable over an increased zone. In addition to this there was bilateral patellar and ankle clonus and a bilateral Babinski sign. The patient was unable to raise his lower limbs in



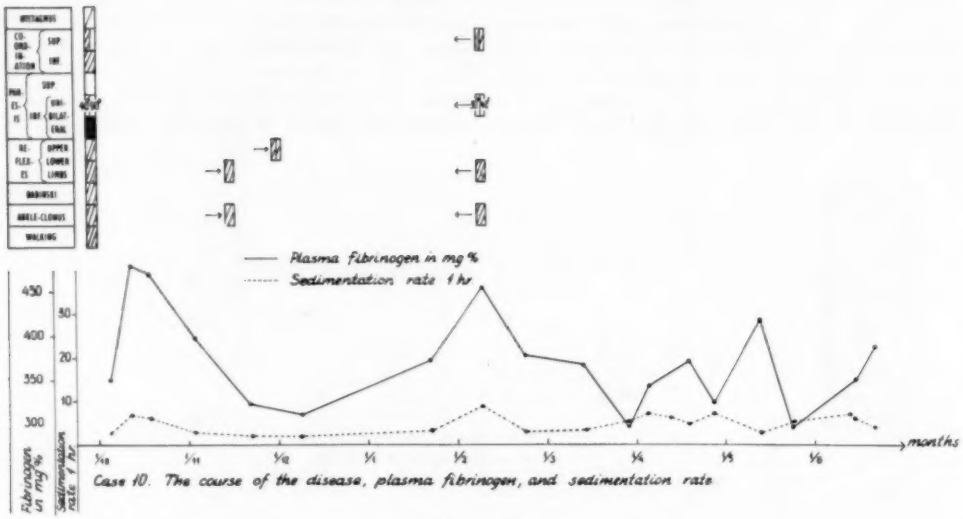
Case 8 The course of the disease, plasma fibrinogen, and sedimentation rate.

Figure 8



Case 9. The course of the disease, plasma fibrinogen, and sedimentation rate.

Figure 9



Case 10. The course of the disease, plasma fibrinogen, and sedimentation rate.

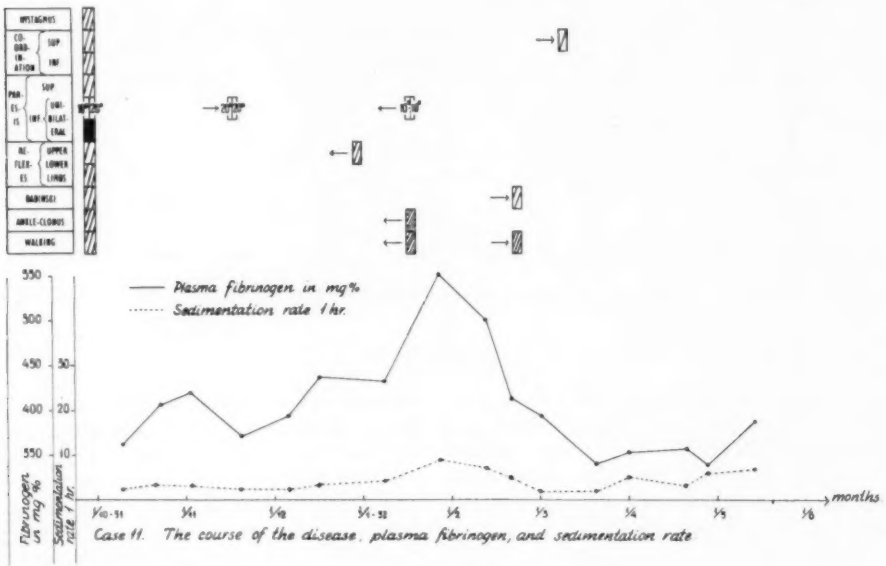
Figure 10

extension from the couch. The gait was very uncertain, and walking was possible only with strong support.

Case 11.—A man aged 54. For a brief period at the age of 30 the patient had transient blurred vision. There were no new symptoms for the following 15 years. After that, in the course of a few months, there developed weakened power in the arms and in the legs, disturbance of balance, and reduced sensibility in the hands, and shortly afterward the gait became uncertain and slow. The following signs were present: Mentally he was euphoric and demented. There was marked nystagmus at the extreme positions of the eyes. Ophthalmoscopy showed bilateral temporal optic atrophy. There was some muscular atrophy in the upper limbs, and the power was diffusely reduced. There was spastic increase of tonus with increased, equal deep reflexes. There was some uncertainty in the finger-to-nose test. The abdominal skin reflexes were weak and equal. There was a marked spastic increase of tone in the lower limbs, with vigorous ankle clonus and brisk, equal deep reflexes. There was a bilateral Babinski

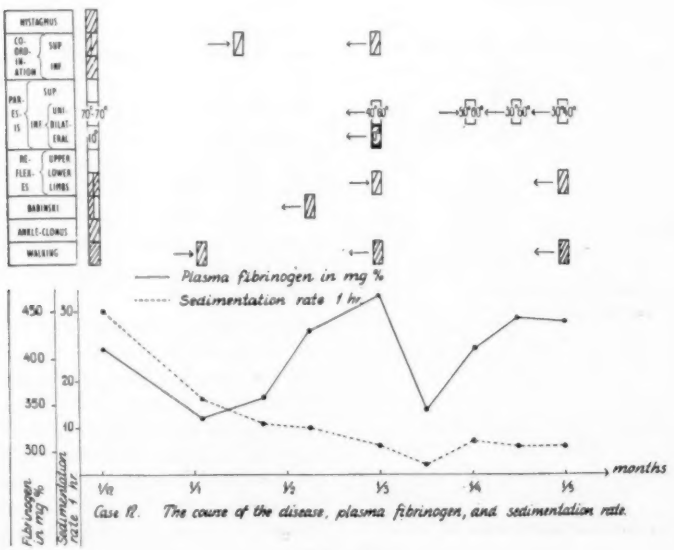
sign. The heel-to-knee test was carried out with considerable uncertainty. The legs could not be raised together in extension, and he could walk only with the help of one person.

CASE 12.—A man aged 34. The first symptoms occurred when the patient was 31 years old, in the form of dizziness and headache; the following year the patient complained of loss of power in the lower limbs. Subsequently the condition progressed rapidly without any considerable remissions. The patient was euphoric. There was gross nystagmus. Ophthalmoscopy showed bilateral temporal optic atrophy. The speech was slightly staccato. There was ataxia in the finger-to-nose test, especially on the right, and dysdiadokokinesia. The abdominal skin reflexes were absent. There was spastic increase of tone in the lower limbs and decreased power. The knee jerks were brisk, with



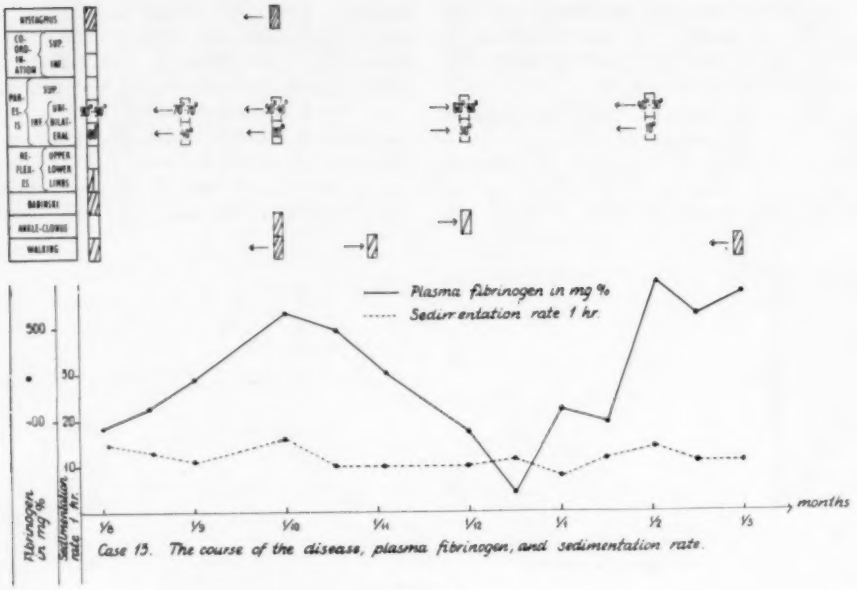
Case 11. The course of the disease, plasma fibrinogen, and sedimentation rate

Figure 11



Case 12. The course of the disease, plasma fibrinogen, and sedimentation rate

Figure 12

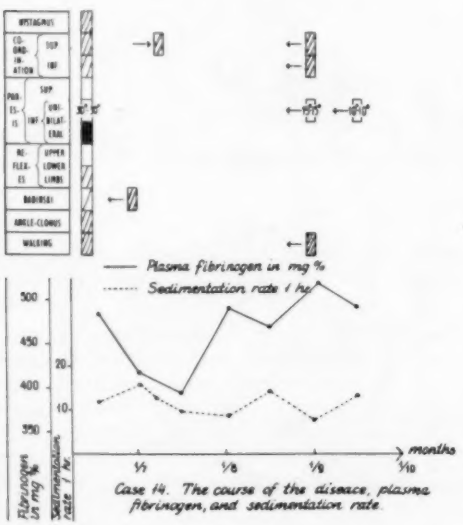


Case 13. The course of the disease, plasma fibrinogen, and sedimentation rate.

Figure 13

slight preponderance on the left side. There was bilateral ankle clonus, and Babinski's sign was present on the right side. There was rather marked ataxia in the heel-to-knee test. The patient could walk only when supported in a walking machine.

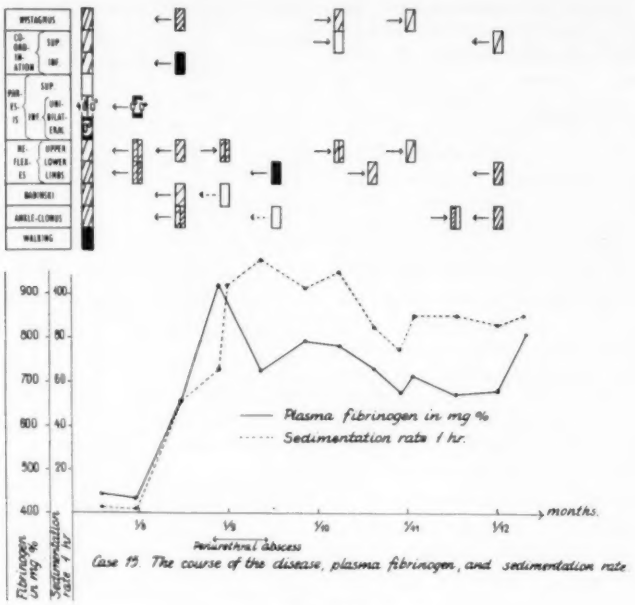
CASE 13.—A man aged 33. When the patient was 21 years of age, diabetes mellitus was diagnosed, and he was consequently treated with a normal diet, without sugar, and insulin. The first symptom of disseminated sclerosis occurred when he was 21 years old. He became totally blind in both eyes, but after an interval of four weeks the sight gradually returned. It was only 10 years later that the patient noticed new symptoms of this disease, in the form of an increasing difficulty in walking. After this the condition worsened relatively rapidly, the course being interrupted only by incomplete remissions. The patient was somewhat euphoric. Movement of the eyes in all directions initiated marked nystagmoid jerks. Ophthalmoscopy showed temporal optic atrophy. The speech was rather staccato. The upper limbs showed nothing abnormal neurologically. The abdominal skin reflexes were absent. On examination of the lower limbs, it was found that the knee jerks were rather brisker on the right than on the left side, and that Babinski's sign was present on both sides; otherwise, the findings were normal. The gait was uncertain and ataxic with somewhat violent movements.



Case 14. The course of the disease, plasma fibrinogen, and sedimentation rate.

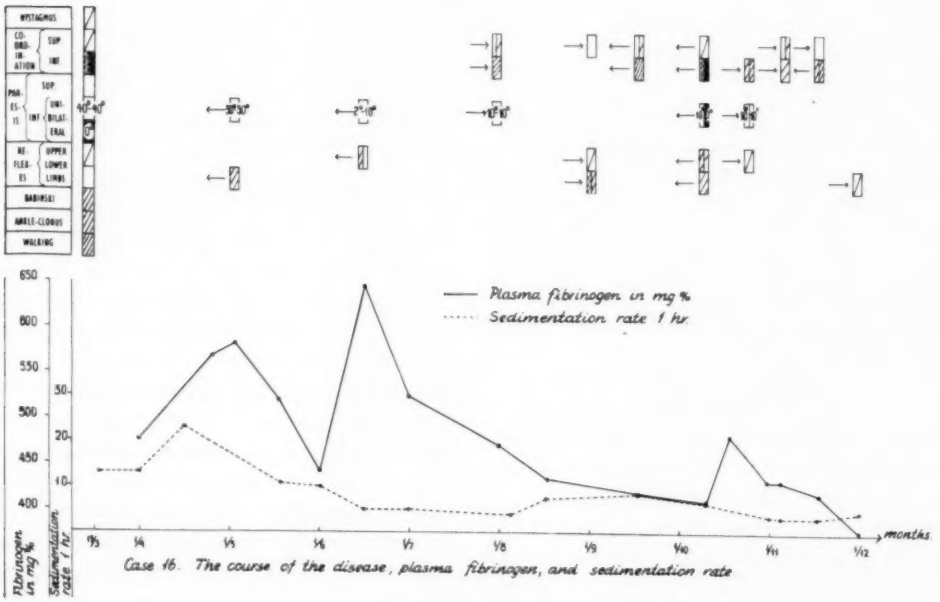
Figure 14

CASE 14.—A man aged 29. The first symptoms of his present illness began when he was 23 years old, in the form of paresthesiae in both lower limbs. Two years later he began to see double, and soon afterward he experienced increasing difficulty in walking. Following this there was rapid progression, even though the condition has been fluctuating. The patient was slightly euphoric. There was marked nystagmus on movement of the eyes in any direction. Ophthalmoscopy showed



Case 15. The course of the disease, plasma fibrinogen, and sedimentation rate

Figure 15



Case 16. The course of the disease, plasma fibrinogen, and sedimentation rate

Figure 16

temporal optic atrophy. The finger-to-nose test demonstrated great uncertainty. The abdominal skin reflexes could not be elicited. There was some spastic increase of tone in the lower limbs. The power was somewhat diffusely reduced. The knee jerks were brisk and equal. There was bilateral ankle clonus and a tendency toward Babinski's response. There was moderate ataxia in the heel-to-knee test. The patient could walk a little with the support of two helpers.

CASE 15.—A man aged 20. The illness had begun about two years previously, with unsteady gait.

At the same time the patient's speech became slow and staccato. The symptoms waned for a short time but soon flared up again. On the whole the condition thereafter worsened, especially in the course of the six months before admission to the hospital. On admission, he was of indifferent mood and mentally of somewhat reduced capacity. There was nystagmus on looking to the right and to the left. Ophthalmoscopy showed no definite optic atrophy. There was slightly increased tonus of the upper limbs, with relatively brisk and equal reflexes. There was some terminal uncertainty in the finger-to-nose test, and, in addition, there was dysdiadokokinesia. There was marked spastic increase of tonus in the lower limbs, and the deep reflexes were brisk and equal. The power was diffusely reduced. There was some uncertainty in the heel-to-knee test. The patient could not walk. While he was in the hospital a periurethral abscess developed (as shown on the curve). However, this resolved in a fortnight.

CASE 16.—A man aged 45. He became ill when he was 28 years old. The first sign of the illness he noticed was the sudden occurrence of loss of power in the lower limbs. The course of the disease has been intermittent, and the condition has gradually worsened. At the start of the investigation the patient was slightly euphoric. There was slight nystagmus on lateral positioning of the eyes. Ophthalmoscopy showed no optic atrophy. On both sides there was slight terminal uncertainty in the finger-to-nose test and some dysdiadokokinesia. The abdominal skin reflexes on the left side were absent. The power in both lower limbs was reduced. The tonus showed marked increase of spasticity, but the deep reflexes were normal. There was a marked ankle clonus and Babinski sign bilaterally. The heel-to-knee test could not be performed at all on the left side and was extremely uncertain on the right. The patient could walk only in the parallel bars.

COMMENT

The investigations here presented seem to show that variations in the plasma fibrinogen occur in the course of multiple sclerosis. Moreover, the investigations suggest that the exacerbations in multiple sclerosis are accompanied by increased plasma fibrinogen. On the other hand, it seems as though not all the periods during which there is a high plasma fibrinogen (also as compared with the sedimentation rate) are accompanied by exacerbations of the disease.

Is the demonstrated rise in the amount of plasma fibrinogen specific for multiple sclerosis, and how much importance can be ascribed to this rise and the fluctuation of the amount of fibrinogen in relation to the pathogenesis of the disease? It has been shown * that in the majority of chronic diseases, inflammatory as well as degenerative, the fibrinogen levels are higher than in normal persons. This means that the increased plasma fibrinogen content in multiple sclerosis cannot be regarded as specific for this disease, as compared with several other chronic diseases. Through their investigations, Ham and Curtis [25] found not only that the sedimentation rate in chronic inflammatory and degenerative diseases depends on the amount of fibrinogen, but that it may also, and to a considerable extent, be influenced by changes in the other serum proteins, which during chronic processes are often permanently altered. The amount of fibrinogen and the sedimentation rate during the course of chronic processes, on the other hand, have not previously been subjected to methodical investigations. However, it has been shown [25] that the plasma fibrinogen content in the normal person is fairly constant, indicating that a rise of 100 mg. per 100 cc. is pathological.

The question is now what importance can be attributed to the variations found in the amount of fibrinogen in plasma. As mentioned, it has been demonstrated [10] that an increase in the content of proteins in plasma with a small negative electric charge, i. e., fibrinogen and globulin, is followed by a decrease in the electric charge of the thrombocytes, which is shown through an increased agglutinability. In the introduction it has also been pointed out that the thrombocytes are able to agglutinate alone and block the vessels, thus producing infarcts,† and that several conditions in connection with multiple sclerosis indicate that the characteristic plaques are caused by thrombocytic thrombi.

Certain circumstances in connection with the investigations here described indicate, however, that the importance attributed to

* References 22 and 25.

† References 7, 8, and 9.

the plasma fibrinogen in the formation of thrombi is best looked upon as that of an accompanying phenomenon to the causative factor.

As will be remembered, it was found, among other things, that, whereas the exacerbations of the disease seemed to be accompanied by a rise in the plasma fibrinogen, there were several instances of an increased plasma fibrinogen without clinical signs of exacerbation. This may be due to the presence of thrombi in "silent zones," or it may be that the thrombi have been too small to cause signs; but it is more likely, still, to be due to the absence of the actual provoking factor in the thrombus formation.

In this connection, Case 6 seems to be especially illustrative. During the period of observation of five months this patient showed two periods of exacerbation. Both were followed by partial remissions. As in the other cases, the plasma fibrinogen content proved to be especially high, as compared with the sedimentation rate, during periods of exacerbation. The last increase in the plasma fibrinogen content, however, shows circumstances of special interest, as this rise occurred in connection with pneumonia. As shown in the curve, this was accompanied by an increased sedimentation rate, as seen in other patients with this disease. Despite the considerable rise in the amount of plasma fibrinogen, there was no simultaneous exacerbation of the patient's neurological disease.

The supposition that the plasma fibrinogen should be of primary importance in the thrombus formation is rendered improbable, moreover, by the increased fibrinogen found in other chronic diseases, in which connection it does not cause an increased frequency of thrombus formation.

The fact that the sedimentation rate is so widely independent of the plasma fibrinogen also indicates that some importance may be attributed to changes in other factors, such as the other serum proteins.

Thus, it seems most probable that the periodically increased plasma fibrinogen content, as well as the clinically demonstrable exacerbations, constitutes only an accompanying phenomenon to the actual cause of the disease.

SUMMARY

On the basis of Putnam's theory that the characteristic plaques in multiple sclerosis are caused by thrombi in the small veins of the central nervous system, investigations have been made with a view to demonstrating factors which might explain the origin of these thrombi.

A rise in the plasma fibrinogen has been demonstrated in multiple sclerosis; this is of special interest in this connection, as a raised fibrinogen content increases the agglutinability of the thrombocytes.

The investigations here described seem to indicate that variations of the plasma fibrinogen occur in multiple sclerosis, and that exacerbations of the disease are accompanied by rises in the plasma fibrinogen.

This gives rise to the question of what importance may be ascribed to the plasma fibrinogen in the case of thrombus formation in plaques. Several conditions, however, seem to go against a possible primary importance of fibrinogen in this process. Thus, often a raised fibrinogen occurred without clinical signs of the formation of new plaques. A raised plasma fibrinogen is, moreover, found in other chronic diseases without this giving rise to an increased frequency of thrombus formation. The periodically raised plasma fibrinogen content, as well as the clinically demonstrable exacerbations, is most likely to be an accompanying phenomenon to the actual cause of the disease.

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Reserpine in the Treatment of Psychotics with Convulsive Disorders

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Reserpine is a crystalline alkaloid isolated from the crude root of Rauwolfia serpentina. The latter drug was used for centuries in native Indian medicine for the treatment of a wide variety of diseases, including mental disorders, but it was introduced into this country for its use in the management of hypertension. Reserpine, isolated in 1952, appears to be the chief active principle of Rauwolfia. The value of resperine in the treatment of disturbed psychiotics has been shown by us in previous papers.* These studies included only a small number of patients with convulsive disorders. However, since there was an indication that such patients did not respond to treatment as well as the others, and since at times the incidence of convulsive seizures seemed to be increased, it was deemed advisable to subject to more intensive study a larger group of patients with convulsive disorders. This study is being reported in the present paper.

SUBJECTS

The patients in this study fall into three groups. In the first group are 11 schizophrenic patients who have had occasional convulsive seizures. The onset of these seizures occurred relatively late in life, between the ages of 25 and 55, except in two cases, in one of which the onset was in early childhood and in the other at the age of 16. Moreover, in only three patients were the convulsions frequent enough to require anticonvulsant medication. The second group consists of 25 patients whose mental symptoms are believed to be secondary either to epilepsy or to mental deficiency. Convulsive seizures in all of these patients began in early life and occurred more frequently than in the first group. All, with but one exception, have required anticonvulsant medication of phenobarbital (Luminal) and/or diphenylhydantoin (Dilantin). The third group includes seven schizophrenic patients who have undergone various forms of psychosurgery (three, topectomies, and four, prefrontal lobotomies) and who have had convulsive seizures at some time following the operation. None of these patients were on anticonvulsant medication at the time of this study.

METHOD OF STUDY

One-milligram tablets of reserpine† and 2-cc. ampuls of parenteral solution containing 2.5 mg. of reserpine per cubic centimeter were used.

The general dosage plan followed was the one described in our previous papers.‡ This plan is outlined as follows:

With the start of therapy the patient received 5 mg. of reserpine intramuscularly and 3 mg. orally each morning. This dosage was continued for 10 days. If by this time the patient was showing a beneficial response (not merely sedation), the oral dose was continued, but the intramuscular dose was given every other day for three doses. Then, if the patient's condition still showed evidence of improvement, the intramuscular dose was given every fourth day for two doses, whereas the daily oral dose was continued. Finally, if the patient's mental state remained favorable, the daily oral dose of 3 mg. was continued, but the intramuscular dose was discontinued as a regular medication, and was given only as a booster dose at such times as the patient became very disturbed.

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* References 1, 2, and 3.

† The reserpine used in this study was supplied by Ciba Pharmaceutical Products, Inc., under the name of Serpasil.

‡ References 2 and 3.

If, after the first 10 days of oral and intramuscular reserpine therapy, the patient did not show a beneficial response, the 3 mg. orally and 5 mg. intramuscularly were continued daily for six more days. If there was still no improvement, the oral dose was maintained, but the intramuscular dose was increased to 10 mg. every other day, and 5 mg. on alternate days. This regimen was carried on for eight days. If there was still no improvement, the daily oral dose of 3 mg. was continued, but the intramuscular dose was raised to 10 mg. daily for five doses. If at the end of this time no improvement was evident in the mental state of the patient, the intramuscular dose was reduced to 5 mg. daily for three doses and then eliminated completely, whereas the daily oral dose of 3 mg. was continued.

An oral dose of 3 mg. was found to be the optimal maintenance dose for most of the patients. However, because of side-reactions, the maintenance dose had to be reduced to 2 mg. in one instance.

All of the patients in this study were started on reserpine therapy at a time when they were disturbed. While receiving reserpine therapy they were given no other somatic therapy or sedative, with the exception of their usual anticonvulsant medication.

It was found in previous studies § that a minimal course of therapy consisted of at least three consecutive months. All of the patients in this study received reserpine from three to six months.

RESULTS

The results of this study have been summarized in the accompanying four Tables. The categories of improvement used in the study are defined as follows: By "markedly improved" is meant that the patient's mental state and behavior have improved to such an extent that with a normal amount of supervision she would be able to adjust adequately outside a hospital; by "moderately improved" is meant that, although the patient is not well enough to live outside of a hospital, her behavior has improved to the extent that she is now usually cooperative and is adjusting fairly well to the hospital environment; by "slightly improved" is meant that the patient is a little easier to manage, but still manifests excited, assaultive, or destructive behavior. The evaluation of the patient in regard to degree of improvement was made by the physician in charge (J. B.), the supervising nurse of the building, and the nurse or attendant in charge of the patient's ward.

Table 1 is an analysis of the improvement in the 43 patients of this study in accordance with the patient's diagnosis. It is seen that only 5% of the total number are markedly improved and 35% moderately improved. This can be contrasted with the results for 159 schizophrenics, reported elsewhere.[3] In the latter study, 22% showed marked improvement, and 41%, moderate improvement. An analysis of the improvement in respect to the present age of the patient appears in Table 2. There is some indication from this analysis that the younger patients are more likely to show a greater improvement. Table 3 presents an analysis of the improvement in accordance with the duration of the present hospitalization, and Table 4 is an analysis of the improvement in accordance with the duration of the patient's psychotic illness as measured from her first hospitalization. There is slight indication from both these Tables that the longer a patient has remained in the hospital, and the longer the patient has been psychotic, the less are her chances of achieving a marked or moderate improvement.

CLINICAL COURSE

In a previous paper [2] Barsa distinguished three stages in the patient's course of therapy with reserpine: the sedative period, the turbulent period, and the integrative period. The sedative period begins very soon after the onset of therapy and is characterized by the sedative effect of the drug, the patient becoming quieter, less disturbed, and perhaps quite drowsy. This usually lasts from 3 to 10 days and is followed by the turbulent period, in which there is increasing tension, anxiety, restlessness; the patient's behavior is more disturbed, and the delusions and hallucinations are often more pronounced. The duration of this period varies from a day to two or three weeks. The successfully treated patient then passes into the integrative period, in which the patient's

§ References 2 and 3.

TABLE 1.—*Improvement in Respect to Diagnosis*

Diagnosis	Markedly Improved	Moderately Improved	Slightly Improved	No Improvement	No. of Cases
Dementia praecox					
Paranoid	.....	2 (50%)	2 (50%)	.....	4
Catatonic	.....	2 (40%)	1 (20%)	2 (40%)	5
Mixed	1 (50%)	1 (50%)	.....	.....	2
Total	1 (9%)	5 (45%)	3 (27%)	2 (18%)	11
Psychosis due to epilepsy					
Deterioration	.....	3 (25%)	7 (58%)	2 (17%)	12
Epileptic clouded states	.....	4 (44%)	4 (44%)	1 (11%)	9
Paranoid type	.....	.....	1 (100%)	.....	1
Total	.....	7 (32%)	12 (55%)	3 (14%)	22
Psychosis with mental deficiency	1 (33%)	2 (67%)	.....	.....	3
Psychosurgery patients	.....	1 (14%)	3 (43%)	3 (43%)	7
Total	2 (5%)	15 (35%)	18 (42%)	8 (19%)	43

TABLE 2.—*Improvement in Respect to Age*

Age	Markedly Improved	Moderately Improved	Slightly Improved	No Improvement	No. of Cases
15-20	1 (33%)	1 (33%)	1 (33%)	.....	3
21-30	1 (8%)	6 (46%)	4 (31%)	2 (15%)	13
31-40	.....	3 (43%)	2 (29%)	2 (29%)	7
41-50	.....	3 (25%)	6 (50%)	3 (25%)	12
51-60	.....	2 (33%)	4 (66%)	.....	6
61-65	.....	.....	1 (50%)	1 (50%)	2

TABLE 3.—*Improvement in Respect to Duration of Present Hospitalization*

Duration of Hospitalization	Markedly Improved	Moderately Improved	Slightly Improved	No Improvement	No. of Cases
Less than 1 yr	.....	.....	1 (100%)	.....	1
1-3 yr	2 (20%)	3 (30%)	2 (20%)	3 (30%)	10
3-5 yr	.....	4 (36%)	6 (55%)	1 (9%)	11
5-10 yr	.....	3 (30%)	5 (50%)	2 (20%)	10
More than 10 yr	.....	5 (45%)	4 (36%)	2 (18%)	11

TABLE 4.—*Improvement in Respect to Duration of Illness as Measured from Time of First Hospitalization*

Duration of Illness from First Hospitalization	Markedly Improved	Moderately Improved	Slightly Improved	No Improvement	No. of Cases
Less than 1 yr	.....	.....	1 (100%)	.....	1
1-3 yr	2 (33%)	2 (33%)	1 (17%)	1 (17%)	6
3-5 yr	.....	1 (20%)	4 (80%)	.....	5
5-10 yr	.....	5 (42%)	5 (42%)	2 (17%)	12
More than 10 yr	.....	7 (37%)	7 (37%)	5 (26%)	19

personality is gradually integrated, and delusions and hallucinations disappear.

Very few of the patients in this study were able to attain the integrative period. The majority of the patients never progressed beyond the sedative period, or, if they did pass into the turbulent period, they were unable to advance, and they returned to the sedative stage. However, the value of the sedative effect should not be underestimated, for it was thereby possible to quiet chronically disturbed, irritable, explosive patients over long periods of time, with no clouding of consciousness and with no impairment in the patient's appetite.

SIDE-REACTIONS

Drowsiness and a sense of fatigue occurred frequently during the sedative period. Generalized tremulousness, increased salivation,

dizziness, edema of the face and feet, frequency of urination, nausea, diarrhea, and paresthesiae of the extremities were often experienced during the early weeks of therapy, especially during the turbulent period. Nasal stuffiness was a frequent complaint. Characteristically an increase in appetite manifested itself very soon in therapy. If the appetite later fell off considerably and became poor, it was usually an indication of overdosage of reserpine.

Two patients in this study developed a typical Parkinsonian syndrome after four and five weeks of therapy. These symptoms were made to disappear merely by reducing the dosage of reserpine.

Ten patients in this study, including two who had had topectomies previously, experienced grand mal convulsive seizures for the first time during the first six weeks of therapy. Electroencephalograms were taken on eight of these patients. The EEG of four patients was considered within normal limits, whereas those of the other four were abnormal and indicative of a convulsive disorder.

In five patients who had had convulsive seizures previously, there was definite increase in seizures during the first six weeks of therapy. This increased incidence of seizures did not occur beyond the first six weeks; in fact, in several patients there was a trend toward decrease of seizures in subsequent months. However, these patients will have to be followed further.

Two patients had a decided increase in seizures during the first weeks immediately following termination of reserpine therapy, and, again, after three months of therapy.

Electroencephalograms || were taken on nine patients just prior to starting treatment All these patients had had frequent seizures in the past. Six of the pre-treatment electroencephalograms were considered within normal limits, and they remained normal after three months of reserpine therapy. Three of the pretreatment electroencephalograms were abnormal and were indicative of a convulsive disorder. One record was read as follows: There is some alpha activity, about 8½ cps; conspicuous in the tracing is the presence of high-amplitude slow waves, 4 cps, and even as slow as 2 cps, a few of which are preceded by spikes; this low activity occurs in bursts which run into each other, so that it is difficult to say where one leaves off and the next begins. After three months this patient's EEG was interpreted as follows: The slow frequencies are much less in evidence in this tracing than they were in the previous recording; the alpha activity is high and somewhat irregular, and 4- to 7-cps activity is prominent; the tracing is still recognizable as epileptic.

Another abnormal pretreatment electroencephalogram was interpreted as follows: Some alpha activity is present; diffuse low-amplitude, 4- to 5-cps activity is mixed with low-amplitude, 15- to 25-cps, rapid activity; one burst of high-amplitude 4- to 5-cps activity is seen; this burst lasts about two seconds. After three months this patient's record was as follows: Normal EEG; low-amplitude, rapid activity; no bursts seen in this tracing.

Another abnormal pretreatment electroencephalogram was as follows: There is little activity within the alpha range; much 6-cps activity is present as the dominant pattern; bursts of 2- to 4-cps waves occur and run into each other, so that their duration is difficult to assess. After three months of therapy this patient's EEG remained essentially the same.

COMMENT

The question arises as to why the mental symptoms of these patients with convulsive disorders did not respond as well to therapy as did those of patients without convulsive seizures. The explanation may be that in the former the mental symptoms, like the seizures, are organically determined and, therefore, not as amenable to drug therapy. Another point to consider is that the paranoid element was usually predominant in the symptomatology of these patients with con-

|| Dr. John L. Simon interpreted the electroencephalograms.

vulsive disorders, and this symptom is known to be particularly resistant to all forms of therapy.

The question also arises as to the etiology of the increased incidence of convulsive seizures during therapy. Is it due to specific convulsant properties of reserpine, or, rather, is it the result of disruption of the body's homeostasis in susceptible persons? The latter explanation seems to be the more plausible, since the increase in seizures did not occur beyond the first six weeks, and since the drug did not produce any abnormal changes in the electroencephalogram. Reference is made to another study,[4] which also revealed no significant changes in the EEG after reserpine therapy.

In treating epileptics with reserpine, it would seem advisable to begin therapy with small oral doses and to build up the dosage gradually. Furthermore, since most epileptics can be expected to show no more than a sedative effect from the drug, the necessity for the intramuscular administration of reserpine would not be present in these cases. Finally, it should be noted that in discontinuation of therapy the drug should be withdrawn very gradually lest convulsive seizures be precipitated.

CONCLUSIONS

Reserpine therapy is not as effective in psychotic patients with convulsive disorders as in psychotics without convulsive seizures. In the former the maximum therapeutic effect to be expected is usually one of sedation.

There is an increased incidence of convulsive seizures during the first six weeks of therapy.

In treating epileptics with reserpine it is recommended that therapy be begun with small oral doses and that the dosage be built up gradually. The necessity for intramuscular administration of reserpine is not present in most cases. Finally, in termination of therapy, the drug should be withdrawn very gradually lest convulsive seizures be precipitated.

Dr. Elizabeth Benforth, Ruth Lee, R.N.; Barbara Kearney, and the entire staff of Building 60 cooperated in this project.

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Chlorpromazine (Thorazine)—Rauwolfia Combination in Neuropsychiatry

Preliminary Report

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The use of chlorpromazine (Thorazine)[1] alone or Rauwolfia serpentina[2] alone in neuropsychiatric conditions has been reported by many authors. At the time of writing, there have been no published reports on the use of the combination of chlorpromazine and Rauwolfia in this type of patient. For the past 18 months this combination has been used with a degree of success in the treatment of moderate and severe essential hypertension.[3] The ease of administration, lack of toxicity and side-effects, and the synergistic therapeutic potentiation suggested the possibility of their simultaneous administration in neuropsychiatric conditions.

This preliminary report is based upon observations on 24 patients with varied neuropsychiatric conditions, none of whom were confined to an institution while receiving this therapy.

METHOD

Preliminary testing with the combination of chlorpromazine and Rauwolfia was begun on patients with schizophrenia, manic-depressive psychosis, senile agitated states, anxiety neuroses, menopausal agitation, epilepsy, primary behavior disorders, and mental deficiency. The subjects were all ambulatory and varied in age from 3 to 92 years.

The diagnosis of each patient had been previously determined by a psychiatrist. All the patients were chronically disturbed, and their behavior patterns had been observed, treated, and documented. Prior therapy included the use of chlorpromazine alone or Rauwolfia sepentina alone, as well as shock therapy, psychoanalysis, barbiturates, and amphetamine.

The patients were placed on the following oral combination:

Chlorpromazine 15.0 mg.

Rauwolfia serpentina 50 mg. (whole root)

The medication was given three to four times daily. In some instances the dose was doubled or tripled. In the cases of smaller, younger patients, the dose was halved. None of the subjects received parenteral treatment. No differences were observed when the whole root of Rauwolfia serpentina was replaced by one of its alkaloids, reserpine.

RESULTS

The patients were observed, first, at weekly intervals and, later, at monthly intervals. Of this preliminary series of 24 patients, there were only 3 who did not improve significantly from the effects of the medication. All the remaining 21 patients demonstrated moderate to marked improvement. Unfortunately, there exists no precise method of grading, but an honest attempt was made to evaluate the response from the patient and the family and other general observations. One possible objective yardstick is the amount of time the patient is asymptomatic without recourse to shock therapy or hospitalization.

During the course of therapy, the patients were given, at one time or another, a placebo of similar size, shape, and color. In most of the cases, after a period of 3 to 12 days of placebo therapy, there was an aggravation of symptoms. No attempt at any statistical evaluation is made in this preliminary report. There will be further statistical evidence upon

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From the New York Medical College, Flower and Fifth Avenue Hospitals.

Results of Combined Chlorpromazine-Rauwolfia Therapy in Neuropsychiatric Patients

No.	Case	Age	Sex	Diagnosis	Previous Treatment	Duration of Chlorpromazine-Rauwolfia Treatment, Mo.	Results
1	K. N.	36	F	Anxiety neurosis	Psychoanalysis Barbiturates Chlorpromazine alone	10	Marked improvement in 3 wk.
2	R. F.	24	F	Schizoid	Shock, lobectomy Barbiturates Institutions	3	Marked improvement in 2 mo.
3	W. B.	6	M	Schizoid	Barbiturates Rauwolfia alone Chlorpromazine alone	6	Dramatic improvement in 1 wk.; able to start school
4	E. S.	33	F	Anxiety neurosis	Barbiturates Psychoanalysis Shock, amphetamine	2	Normal behavior in 3 wk.
5	H. P.	3	F	Schizoid	Institution Rauwolfia alone Chlorpromazine alone	6	Slight improvement after 3 mo.
6	S. R.	46	F	Suicidal	Psychoanalysis Barbiturates Chlorpromazine alone Rauwolfia alone	12	Improved while on combined chlorpromazine-Rauwolfia; no carry-over
7	Z. M.	66	F	Anxiety Senile	Shock Barbiturates	2	Marked improvement in 2 wk.
8	R. M.	42	F	Suicidal	Barbiturates Psychoanalysis Institutions	7	Marked improvement in 5 wk.
9	C. B.	36	F	Depression	Barbiturates Shock Rauwolfia alone Chlorpromazine alone	1	Marked improvement in 8 days
10	L. S.	54	F	Anxiety Senile	Barbiturates Amphetamines	10	Marked improvement in 1 mo.
11	D. J.	42	F	Menopausal	Shock Barbiturates Institution	2	Requested and received shock therapy; very little improvement
12	G. B.	44	F	Anxiety Neurosis Suicidal	Shock Institution Barbiturates	6	Normal behavior after 2 wk.
13	S. J.	38	F	Anxiety neurosis	Psychoanalysis Barbiturates Chlorpromazine alone Rauwolfia alone	4	Dramatic improvement in 4 wk.
14	W. A.	43	F	Anxiety neurosis	Barbiturates Amphetamine	13	Marked improvement in 3 wk.
15	R. I.	69	M	Anxiety	Barbiturates	4	Moderate improvement in 2 mo.
16	S. I.	50	F	Menopausal	Barbiturates Chlorpromazine alone	12	Marked improvement in 3 wk.
17	R. H.	33	M	Colitis	Institution Barbiturates	2	Diarrhea worse
18	M. F.	39	M	Anxiety neurosis	Institution Barbiturates Chlorpromazine alone	6	Moderate improvement
19	P. J.	32	M	Functional G. I. disease	Antispasmodics Barbiturates	1	No improvement
20	R. R.	92	F	Anxiety Senile	Choral hydrate Amphetamine Chlorpromazine alone	1	Improvement no greater than with chlorpromazine alone
21	F. B.	60	F	Menopausal	Barbiturates Rauwolfia alone	2 wk.	No improvement; shock therapy required
22	C. P.	44	F	Anxiety neurosis	Barbiturates	10	Dramatic improvement in 10 days
23	C. F.	48	F	Anxiety neurosis	Psychoanalysis Barbiturates Amphetamine Rauwolfia alone	3	Moderate improvement; no greater than with Rauwolfia alone
24	B. M.	52	F	Epilepsy	Barbiturates Diphenylhydantoin Rauwolfia alone	2	Fewer seizures and less anxiety than with Rauwolfia alone

the completion of large-scale studies now being conducted in outpatient departments and psychiatric institutions.

Several cases are briefly presented.

CASE 1.—K. N.; anxiety neurosis. A 36-year-old sister of a physician. She had received large doses of barbiturates and amphetamines from her psychoanalyst over a period of nine years. She had a severe anxiety neurosis, was unable to cope with the family, and remained almost constantly confined to her home. She was unable to stay alone, and insomnia was a besetting problem. There was moderate improvement with 300 mg. of chlorpromazine daily alone. Three weeks after the onset of therapy with chlorpromazine and Rauwolfia, her family relationship improved; she could sleep with no sedation, go to the movies, and visit friends. There has been steady improvement over a period of 10 months.

CASE 2.—R. F.; schizophrenia. A 24-year-old unmarried woman with a psychiatric history dating back to childhood. She had spent four years in mental institutions, had received several courses of electroshock, and had a lobectomy seven years before. She had been unable to remain away from a mental hospital for more than six months. Results with Rauwolfia alone, and with chlorpromazine alone, were encouraging. Treatment with a combination of the two for a period of two months was rewarded by the ability of the patient to assume a position in her father's store, where she is happy and working satisfactorily.

CASE 3.—W. B.; schizophrenia. This 6-year-old boy has been disturbed since infancy. He was destructive, agitated, and uncooperative and could not attend school. There was almost no response to either 100 mg. of chlorpromazine daily or 2.0 mg. of reserpine daily when given singly. One week after start of combined chlorpromazine-Rauwolfia therapy he became more docile and manageable. Two months later he made a fair adjustment in school. Five days after placebo therapy he reverted to an agitated state but was under control within 48 hours after the medication was restored.

CASE 6.—R. S.; anxiety neurosis. A 46-year-old woman, separated from her husband, made four suicidal attempts within seven years; she was constantly melancholic and frigid. She showed greater improvement while on combined chlorpromazine-Rauwolfia therapy than when taking either agent singly. She went out of town for a period of one month, during which she neglected to take the medication. Upon her return she took an overdose of barbiturates. Therapy was reinstituted, and she apparently now realizes the importance of continuing with the medication.

CASE 11.—D. J.; severe menopausal symptoms. A 42-year-old woman with marked depression after an artificial menopause. After two months of therapy with both preparations she felt that her improvement was too slow and requested shock therapy. It was thought that there was some degree of amelioration, inasmuch as this patient had requested shock on her own volition.

COMMENT

It is recognized that the psychological treatment of mental illness is dependent on value judgment that the patient is able to exercise as he becomes increasingly aware of the nature of his problems. This raises many questions regarding the use of pharmacological agents, which in many ways diminish value judgments. We do not know, for example, the exact effect of the combination of chlorpromazine and Rauwolfia on the brain. It is possible that this combination may act as a temporary depressant of the frontal lobes of the brain or of the corticothalamic tracts.

There are tremendous difficulties in achieving satisfactory results through the use of psychological treatment alone.

There is also no attempt to minimize the fact that we are dealing with a combination of agents which may hamper judgment, nor is there any attempt on the grounds of expediency to apologize for the use of such agents. There are limitations of psychotherapeutic procedures, as well as limitations of chemical procedures, but it is felt, however, that in this small series of cases a combination of therapeutic agents has been employed that is exceedingly effective in the treatment of many mental conditions.

Of the 21 patients improved, there were 11 who had received chlorpromazine or Rauwolfia singly with moderate improvement. Nine of these 11 showed greater tranquillity, less anxiety, increased cooperation, and fewer symptoms when taking the two agents concurrently.

There were no significant side-effects to warrant cessation of therapy in any of the cases. No jaundice or other toxic manifestation was encountered or reported.

CONCLUSIONS

For the first time, a combination of two therapeutic agents, chlorpromazine and Rauwolfia, is reported for the use of varied neuropsychiatric conditions. It is felt that the two agents, either of which is moderately beneficial when used singly, are mutually synergistic. The marked improvement noted in 21 of the 24 cases suggests the effectiveness of this combination and the advantages over the use of either agent when employed alone. The possibility that this combination may act as a chemical agent on the corticothalamic centers, enabling patients to function at a more satisfactory level, is suggested. The simultaneous use of the two medications appears to be of greater value than when either agent is used singly.

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The Rapid Intravenous Glucose Tolerance Test in Psychiatric Patients

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A number of reports have appeared in the literature describing abnormal glucose tolerance in various mental disorders as measured by reduction in tolerance for ingested sugar. Carbohydrate metabolism is extremely complex and is interrelated with the fat and protein metabolism as well as with mineral metabolism. The measurement of one particular phase of carbohydrate metabolism by observation of the manner in which the organism utilizes a given amount of sugar gives rise to speculation that changes are occurring throughout the body, both within the cells and in the extracellular fluids, influencing all the metabolic processes in a chain reaction type of circuits and cycles. To date, no means of measuring total metabolism has been devised, and we must content ourselves with the piecemeal type of approach, subject to our limited techniques, and attempt to draw workable conclusions. The relationship between carbohydrate metabolism and mental illness became apparent first in 1928, when Manfred Sakel observed that long periods of insulin-induced hypoglycemia influenced mental symptoms. The exact nature of these changes is not known, but it is established that glucose is the only source of metabolic fuel utilized by the cells of the central nervous system, and alterations in its availability may act as a depressant, or in some way alter the internal chemical reactions of the cells of the central nervous system. It therefore has seemed a logical step to study possible abnormalities in bodily reaction to ingested or injected glucose in patients with mental illness.

The purpose of the present investigation is to evaluate glucose utilization in psychiatric patients by employing the rapid intravenous glucose tolerance test (RIGTT) reported upon in previous publications.*

METHOD AND MATERIAL

Subjects.—Subjects for the study were selected by history and physical examination from patients on the psychiatric service of the Minneapolis VA Hospital. Testing was carried out after the patients had been admitted and were on the standard 2700 Cal. hospital diet for a minimum of three days. No patients with a history of malnutrition prior to admission were included, nor were patients with a family history of diabetes. Concurrent situations known to alter the glucose tolerance test, such as diabetes, liver disease, uremia, postoperative state, and thyroid disorders, were ruled out prior to testing. The test was performed on 30 men with a diagnosis of psychoneurosis and 14 men with schizophrenia. The ages of the patients in both groups were from 21 to 45 years of age. One schizophrenic patient was 62. Psychiatric diagnoses were based upon history, clinical observation, and examination, as well as psychological testing. All patients were sufficiently incapacitated by their illness to require hospitalization.

Experimental Method.—The subjects were in a basal state after a 14-hour fast when the experiments were performed. The method of the RIGTT, described and validated in previous publications,* was employed in exactly the same manner in the present study, except that 50 ml. of blood was drawn from the antecubital vein just prior to injection of the dextrose solution, for the purpose of determining the following serum electrolytes: phosphorus, calcium, sodium, potassium, and magnesium. The actual determinations of these were made by methods routinely used in the clinical chemistry laboratories of the Minneapolis VA Hospital.

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From the Psychiatric Service, VA Hospital, and the Departments of Medicine and Psychiatry, University of Minnesota.

* References 3 and 4.

RESULTS

In Table 1 the results of the RIGTT in psychoneurotic and schizophrenic patients are shown. The normal range for rate of removal of excess glucose from the blood is 3.00% to 4.84% per minute.[4] In the psychoneurotic patient group the range was from 1.09% to 5.54% per minute, with a mean rate of 2.83%. The schizophrenic patients showed a range of 1.54% to 5.77% per minute, with a mean of 3.51%, which lies in the normal range.

In evaluating these results statistically, it was noted that in making a graphic representation of distribution of the normals, as well as of the patients tested, there was marked skewing of the curve. It was therefore felt that the commonly used *t* test would not give as accurate an evaluation of the data as a nonparametric test, such as the Mann-Whitney *U* test. The latter was applied to compare normals with psychoneurotics, normals with psychotics, and psychoneurotics with psychotics. In the first group (normals versus psychoneurotics), the value of *U* was 437 and the mean (mn/2) was 1085. The standard deviation was found to be 136.4. The value of *U* was then 4.75 standard deviations removed from the mean, and the differences noted are therefore highly significant (beyond the 0.001 level). The probability level used throughout was 0.05.

TABLE 1.—*Rate of Removal of Excess Glucose, Per Cent per Minute*

Psychoneurotic Patients					
1	5.54	11	2.84	21	2.27
2	5.21	12	2.82	22	2.16
3	4.95	13	2.79	23	2.10
4	4.07	14	2.79	24	2.10
5	3.85	15	2.52	25	1.98
6	3.68	16	2.47	26	1.98
7	3.68	17	2.43	27	1.95
8	3.38	18	2.40	28	1.89
9	3.15	19	2.39	29	1.80
10	3.15	20	2.39	30	1.73
				31	1.09
Schizophrenic Patients					
1	5.77	6	3.96	11	2.57
2	4.62	7	3.59	12	2.56
3	4.33	8	3.55	13	1.71
4	4.07	9	3.46	14	1.54
5	3.96	10	3.46		

The results for the psychotics versus the normals were evaluated with the same statistical technique, and *U* was found to be 478.5, with a mean of 490 and a standard deviation of 83.3. Thus, *U* is less than 1.96 standard deviations removed from the mean and is not significant at the 0.05 level.

In comparing neurotic with psychotic patients, *U* was found to be 2.046 standard deviations from the mean, and is therefore significant at the 0.05 level of probability.

Tables 2 and 3 summarize the results of electrolyte determinations made at the time the RIGTT was performed. No deviations from the normal ranges of value for each of the electrolytes were found in either group of patients.

COMMENT

These findings indicate that disturbance in glucose tolerance as measured by the RIGTT is present in a highly significant number of psychoneurotic patients, but that this same disturbance is not significantly present in schizophrenic patients. There are many references in the literature indicating that changes in glucose tolerance are found in all mental disorders and are related, hypothetically, to the stress situations predominant in mental illness. No previous studies have utilized the test employed in the present investigation, but results can be compared, since the test used herein determines the biochemical reaction to a given amount of glucose, just like standard glucose tolerance tests.

Aldrich [1] studied a group of 102 acutely psychotic patients who had either recovered completely or lapsed into chronic psychosis. He used the Exton-Rose oral glucose tolerance test (GTT) and reported that approximately 50% of the patients initially tested had abnormal responses to glucose ingestion. There was no definite relationship between the glucose tolerance test and acuteness of illness or response to electroshock therapy.

Studies have also been made on senile patients as compared with schizophrenic

TABLE 2.—*Serum Electrolytes and Rate of Removal of Excess Glucose in Psychoneurotic Patients*

		GTT	P	Ca	Na	K	Mg
	Normal values	3.00-4.84	3-4.5	9-11	138-148	3.9-5.6	1.7-2.3
		%/Min.	Mg./100 Cc.	Mg./100 Cc.	mEq./L	mEq./L	mEq./L
1	J. V.	5.54	2.85	10.5	142	4.7	1.7
2	F. H.	5.21	3.6	10.8	156	5.5	2.5
3	G. W.	4.95	3.6	13.2	140	5.8	3.4
4	J. K.	4.07	4.3	10.3	142	4.7	2.4
5	R. S.	3.85	3.3	11.0	148	4.7	2.3
6	P. L.	3.85	3.1	10.5	140	4.4	2.1
7	M. D.	3.68	3.9	10.5	142	4.8	2.0
8	A. Y.	3.38	3.4	11.0	150	5.6	2.6
9	R. L.	3.15	4.3	9.9	147	5.6	2.3
10	M. S.	3.15	3.4	10.5	147	4.3	2.1
11	C. H.	2.84	4.3	11.8	...	5.5	2.8
12	F. A.	2.82	4.6	10.1	145	4.4	2.0
13	G. M.	2.79	4.0	10.0	160	5.5	2.6
14	F. M.	2.79	3.2	10.2	146	3.9	2.0
15	M. F.	2.52	4.25	12.3	160	3.9	2.5
16	G. S.	2.47	3.4	10.7	146	4.5	2.3
17	J. H.	2.43	3.2	10.3	141	4.2	2.1
18	F. O.	2.40	3.0	9.8	142	4.5	1.9
19	R. H.	2.39	3.6	12.3	146	4.5	2.0
20	M. G.	2.39	4.0	10.1	140	4.3	2.3
21	M. M.	2.27	3.7	10.8	146	4.9	2.3
22	T. M.	2.16	4.0	10.6	146	4.4	2.3
23	R. C.	2.10	3.2	9.5	148	4.5	2.1
24	C. G.	2.10	4.0	10.2	150	4.4	1.8
25	D. R.	1.98	3.4	10.5	147	4.9	2.0
26	L. C.	1.98	3.3	10.5	146	4.8	2.1
27	E. C.	1.95	3.1	10.8	149	4.8	2.3
28	L. G.	1.89	3.0	10.1	146	4.9	2.1
29	R. K.	1.80	3.0	10.1	146	4.3	2.3
30	H. F.	1.73	3.7	9.5	138	4.2	2.0
31	K. O.	1.09	3.0	10.5	149	4.5	2.2

TABLE 3.—*Serum Electrolytes and Rate of Removal of Excess Glucose in Schizophrenic Patients*

		GTT	P	Ca	Na	K	Mg
	Normal values	3.00-4.84	3-4.5	9-11	138-148	3.9-5.6	1.7-2.3
		%/Min.	Mg./100 Cc.	Mg./100 Cc.	mEq./L	mEq./L	mEq./L
1	C. D.	5.77	3.5	9.8	138	4.2	1.8
2	S. S.	4.62	3.1	10.0	162	5.6	2.4
3	C. F.	4.33	4.2	9.4	140	4.7	2.2
4	G. M.	4.07	3.5	10.6	140	4.8	2.1
5	J. M.	3.96	3.2	10.3	142	4.2	2.2
6	P. M.	3.96	3.7	12.9	160	5.0	2.3
7	A. T.	3.59	3.7	10.2	150	5.2	2.4
8	D. G.	3.55	4.2	10.7	145	4.5	2.1
9	M. M.	3.46	3.6	10.4	138	4.0	2.5
10	J. A.	3.46	4.0	9.8	147	4.2	2.0
11	H. C.	2.57	3.6	10.7	156	5.8	2.8
12	J. M.	2.56	3.4	9.9	146	4.5	2.3
13	F. B.	1.71	3.0	10.6	142	4.7	2.3
14	J. J.	1.54	2.85	10.5	146	4.2	2.1

patients. Simon and Garvey [14] reported on use of the Exton-Rose GTT in 28 patients with chronic schizophrenia and 10 patients with senile psychosis. Their results indicated abnormal glucose tolerance in 67.9% of the schizophrenic patients and 80% in the senile psychotic group. Meduna and Vaichulis [13] had previously reported that diabetic-like glucose tolerance curves were obtained in 60% of unselected schizophrenics tested by them.

Altschule and associates [2] attempted to utilize these changes in glucose tolerance in assaying results following electroshock therapy, and they concluded that the GTT cannot be used as an objective index of im-

provement. The changes noted were inconsistent, and the probability of concurrent adrenocortical stimulation altering the glucose tolerance was discussed. Freeman and Zaborenke,[8] in an earlier paper, had arrived at similar conclusions regarding the lack of correlation between improvement of glucose tolerance and state of the mental illness. However, they believed the abnormality in glucose tolerance was due to anxiety and emotional tension associated with the mental condition.

Amatuzio, Schultz, Vanderbilt, Rames, and Nesbitt [3] studied the effect of epinephrine on the RIGTT and found it produced a marked decrease in the blood glucose disappearance rate. The physiological symptoms of anxiety (tremulousness, perspiration, palpitation, apprehension, heightened blood pressure, and tachycardia) are identical with the symptoms produced by administration of epinephrine. Elevation of blood lactic acid is known to follow an injection of epinephrine, and elevated levels of lactic acid have been observed in patients with chronic anxiety. The increased blood sugar presumably is the result of direct action of epinephrine on the liver with increased glycogenolysis, plus an effect on the carbohydrate metabolism secondary to stimulation of the adrenal cortex. This may occur via stimulation of the hypothalamus by epinephrine and subsequent stimulation of the anterior pituitary. The latter, in turn, activates via the pituitary adrenocorticotropic hormone the adrenal cortex, which liberates 17-hydrocorticosterone or 11-dehydro-17-hydroxycorticosterone. These compounds act directly or indirectly as "anti-insulin" substances.

Cronk [5] studied 45 patients who complained of chronic fatigue, which developed insidiously and was aggravated by unpleasant environmental situations. Glucose tolerance curves were flat, even though the fasting blood sugar levels were normal. One could postulate that in these patients chronic stress led to "exhaustion" of the adrenal cortex, or that these patients had a subnormal response to stress and the "anti-insulin" substances were not liberated in sufficient quantities to elevate blood glucose. This type of response may account for the three neurotic patients and the one schizophrenic patient in our series whose rates of removal of excess glucose were above the normal upper limit of 4.8% per minute. Oral glucose tolerance curves in these patients would have been "flat."

Fasting blood sugar levels for schizophrenic patients usually are within normal limits.[10] Meduna and Vaichulis [13] believe that diabetic-like sugar tolerance curves in schizophrenic patients are due to delayed and diminished action of insulin, on the basis of hyperactivity of an anti-insulin factor, a product of the anterior lobe of the pituitary. They have described a hyperglycemic factor in the urine of schizophrenic patients which, when injected intraperitoneally into rabbits, increased their blood sugar markedly. They postulated a specific type of mental disorder characterized by pathological carbohydrate metabolism, as indicated by a pseudodiabetic reaction to the Exton-Rose test, protracted sugar tolerance curves, and the presence of an anti-insulin factor in the urine. Meduna named this disease oneirophrenia.

Goldner and Ricketts [12] attempted to repeat Meduna's experiments, but their results were not in agreement, and they failed to demonstrate the presence of a specific anti-insulin factor in schizophrenics. They found notable variations among their patients, as well as individual differences in the same patient from day to day.

In a recent review of the literature concerning a hyperglycemic-glycogenolytic hormone of the pancreas (labeled glucagon), Foa [6] presents the theory that glucagon formation most probably occurs in the alpha cells of the pancreas. Chemically, this hormone is a protein having a probable molecular weight of 6000 to 8000 and containing all of the amino acids present in the insulin molecule except proline, isoleucine, and cystine. Two amino acids (methionine and tryptophan) not found in insulin are also present in glucagon. Increased quantities of glucagon-like materials have been isolated in the urine of patients having oneirophrenia,[13]

and the inference is drawn that in these patients either excessive stimulation or abnormality of the alpha cells of the pancreas exists. It is not unreasonable to hypothesize that a similar situation may exist in a number of anxious and schizophrenic patients, which may be responsible for the abnormal glucose tolerance response. Furthermore, speculation may be warranted in connection with the variable response of schizophrenic patients to insulin coma therapy, especially with reference to insulin resistance. It is possible that glucagon (anti-insulin hormone) may act to oppose insulin action and account for insulin resistance frequently observed in schizophrenic patients.

Gellhorn, Feldman, and Allen [11] obtained an increase in blood insulin of psychotic patients with a hypoglycemic effect when the patients were under stress of excitement, but in the quiet state the insulin content did not differ from that of normal subjects.

Freeman and Elmadjian [9] investigated the relation between dysfunction in sugar metabolism and reduced adrenal activity and arrived at the hypothesis that the schizophrenic patient suffers from an adrenocortical deficiency and that in chronic cases there may be irreversible physiological changes. In a more recent study, these same investigators [7] again studied the relation of the adrenal cortex to carbohydrate metabolism in schizophrenic patients and concluded that in this disorder there is a reduction of tolerance to glucose and a deficient response of the adrenal cortex to stimulation through the ingestion of sugar. Freeman and Elmadjian have found abnormal sugar tolerances as frequent in chronic as in acute schizophrenia, but they leave unanswered the question whether the phenomenon is due to primary deficiency or is the result of exhaustion following chronic overstimulation from severe emotional tension.

Our results do not clarify the mechanism of the reduction in tolerance to glucose in mental disorders, whether primarily the result of direct action of epinephrine on the liver, or the effect of adrenocortical function, or both. However, the differences between psychoneurotics and schizophrenics in removal rate of excess glucose, as tested with the RIGTT and evaluated with special statistical techniques, can be correlated with clinical findings commonly observed. Anxiety is usually present in greater degree in psychoneurotic patients, while in schizophrenic patients anxiety is often diminished or absent, as manifested by flattened affectivity, whether due to constitutionally weak ego strength or acquired depletion leading to exhaustion, psychologically and physiologically.

SUMMARY

Thirty male psychoneurotic patients and 14 male schizophrenic patients were studied with the rapid intravenous glucose tolerance test (RIGTT).

The psychoneurotic patients showed a mean rate of removal of excess glucose from the blood of 2.83%, slightly below the established minimum in normals.

The schizophrenic patients had a mean rate of 3.51%, considered within the normal range.

Statistical evaluation, using the Mann-Whitney *U* test, reveals highly significant differences between normals and psychoneurotics, beyond the 0.001 level of probability. However, in comparing schizophrenics with normals, the standard deviation is not significant at the 0.05 level.

No abnormal values for the following electrolytes were found in either group of patients: phosphorus, calcium, sodium, potassium, and magnesium.

It appears that the diminished removal of excess glucose is related to the greater degree of anxiety in psychoneurotics, as compared with absence of or diminished anxiety in schizophrenics.

A review and discussion of applicable literature concerning glucose tolerance in mental disorders are included.

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The Clinical Syndrome of Aneurysm of the Middle Cerebral Artery

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The clinical syndrome of aneurysm of the middle cerebral artery is poorly defined. Though many cases of aneurysm of this artery have been recorded, they represent for the most part instances in which the aneurysm has been found at autopsy. Clinical correlations have been notably lacking. For this reason, we have analyzed 12 cases of aneurysm of the middle cerebral artery verified at operation or autopsy in order to define the clinical syndrome and to determine, if possible, the criteria whereby the diagnosis may be established before rupture.

REPORT OF CASES

CASE 1.—J. M.; No. LH 2240.

History.—The patient, a 48-year-old white married man, was admitted to the St. Luke's and Children's Medical Center on April 19, 1948, because of a generalized convulsion, followed by weakness of the right leg and severe, constant, throbbing headache, which was most prominent in the occipital region. Lumbar puncture immediately after admission revealed bloody spinal fluid under a pressure of 28 mm. of mercury. The symptoms gradually improved in the course of two weeks, but upon discharge from the hospital mild headache was still present. A week later the headache became severer, and throbbing tended to be most prominent in the back of the head. Again, the headache became less severe after two weeks of treatment by his local physician, but it was present intermittently until July 11 (three months after onset), when he was readmitted to the St. Luke's and Children's Medical Center in a coma which followed a severe throbbing headache and convulsion. Again, the spinal fluid was bloody and under a pressure of 26 mm. of mercury. The patient was transferred on July 16 to the neurologic service of the Jefferson Medical College Hospital for further study and treatment. The past medical history was negative except for a mastoidectomy and a hemorrhoidectomy in 1937. The patient's father had died of apoplexy. The general physical examination was normal.

Neurologic Examination.—Findings on admission to the Jefferson Hospital were nuchal rigidity; bilateral Kernig sign; retinal arteriosclerosis; blurring of the margins of the optic discs, more prominent on the left side; right homonymous hemianopsia by confrontation; inability to rotate the left eye outward, with diplopia on looking to the left; weakness of retraction of the left angle of the mouth, and generally absent deep tendon reflexes. There was no focal limb weakness.

Laboratory Studies.—Urinalysis on admission revealed 2+ albumin; repeated urinalyses thereafter were normal. The blood count showed 71% hemoglobin; 4,000,000 red cells, and 13,400 white cells, of which 88% were segmented neutrophiles, 11% lymphocytes, and 1% eosinophiles. The Wassermann and Kahn reactions of the blood were negative. Lumbar puncture on July 16 revealed a bloody spinal fluid under an initial pressure of 350 mm. of water. Another spinal fluid examination, on July 31, revealed an xanthochromic fluid under pressure of 130 mm. of water; there were 13 cells per cubic millimeter; the total protein was 158 mg. per 100 cc.; the Wassermann reaction was negative, and the colloidal gold curve 0000000000. The electroencephalogram revealed a low-voltage, 8/sec. record with the voltage somewhat lower over the right hemisphere than the left; there no focal changes. The roentgenogram of the skull was negative.

Course.—The nuchal rigidity and Kernig sign persisted, and the right homonymous hemianopsia and weakness of retraction of the left angle of the mouth remained constant. The paralysis of the left abducens nerve disappeared in the course of

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four days. Perimetric studies revealed concentric constriction of the visual fields, but hemianopsia was present in the right homonymous fields. A bilateral internal carotid arteriography was performed, and a pedunculated intracranial aneurysm arising from the left middle cerebral artery was demonstrated (Fig. 1). On Aug. 16, about one month after the patient's admission to the Jefferson Hospital, Dr. Rudolph Jaeger performed a left frontal craniotomy. Operation revealed a huge amount of macerated brain and blood clot at the base of the frontal lobe. The lower half of the frontal lobe was completely destroyed by hemorrhage. On exposure of the left internal carotid artery and optic nerve, an aneurysm, irregular in shape and composed of two bulbous dilatations, was found emerging from the first part of the

Fig. 1 (Case 1).—Left carotid arteriogram showing aneurysm arising from left middle cerebral artery.

internal carotid artery. One bulbous portion was apparently a newly formed clot where a recent rupture had occurred, and the other represented the dilatation of the artery. The left middle cerebral artery could be seen to come off the aneurysmal dilatation. Apparently, it ran directly from the aneurysm, and there was no evidence of origin of the aneurysm from the carotid. The left anterior cerebral artery could also be seen coming out of the aneurysm. Since the aneurysm could not be isolated from the internal carotid and middle cerebral arteries, it was thought too dangerous to attempt ligation of the internal carotid, middle cerebral, and anterior cerebral arteries, which would be necessary to remove it. The patient's postoperative course was stormy and complicated by pneumonitis, but he recovered and left the hospital in good condition.

CASE 2.—H. H.; No. DH 11377.

History.—The patient, a 53-year-old white woman who was employed as a recorder, was admitted on April 23, 1941. She had collapsed on the street and was brought to the receiving ward by the police. She was unconscious; her skin was cold and clammy; her breathing was stertorous; a frothy red sputum was drooling out of her mouth. Loud, bubbling rales were heard throughout her chest, and her heart sounds could not be heard. There was flaccid paralysis of all the limbs. The blood pressure on admission was 170/120. An incomplete past medical history was obtained from the patient's sister, who stated that the patient had had high blood pressure for several years. She had had a pelvic operation for a uterine tumor eight years previously. She had been well except for a mild chest cold three weeks before admission.

Neurologic Examination.—The patient could be awakened but was confused and incontinent. The fundi showed marked arterial spasm and a petechial hemorrhage in the right eye. The limbs were flaccid but could be moved voluntarily in response to painful stimuli. All the deep tendon reflexes were absent. Nuchal rigidity and a bilateral Kernig sign were present. Examination, three days after entrance, revealed slight weakness of both legs, more marked on the left, and difficulty in performing the heel-knee tests, particularly with the left leg. The ophthalmologic consultant reported hypertensive retinitis with advanced arteriosclerosis.

Laboratory Studies.—Urinalysis on admission revealed 4+ albumin, 2+ sugar, 20 pus cells per cubic millimeter, and a few casts. On repeated examination, the albumin reaction ranged from 2+ to 3+ and casts were present, but no sugar was found. The blood count on her admission to the hospital showed hemoglobin of 120%, 6,000,000 red cells, and 7200 white cells. Two days later the blood count revealed 94% hemoglobin, 4,750,000 red blood cells, and 14,500 white blood cells, of which 89% were neutrophiles and 11% were lymphocytes. The Wassermann and Kahn reactions of the blood were negative. Upon repeated examinations, the blood sugar ranged from 77 to 170 mg. per 100 cc.; the carbon-dioxide capacity, from 31.5 to 51 vol. %. The initial lumbar puncture revealed a grossly bloody spinal fluid under a pressure of 300 mm. of water. Repeated lumbar punctures thereafter always yielded bloody fluids. The electrocardiogram showed a left axis deviation and a late inversion of the T-wave.

Course.—The patient's state of consciousness showed progressive improvement while she was in the hospital. Her temperature, however, remained elevated, ranging from 100 to 103 F; the pulse rate

varied from 90 to 120 per minute, and respirations from 24 to 30 per minute. The blood pressure ranged from 100-140/70-90. Without apparent cause, she became progressively more stuporous, her respirations became impaired, and she died on May 4, the 12th day of her illness.

Autopsy.—Necropsy revealed pulmonary congestion and edema and partial pulmonary atelectasis. Inspection of the brain showed sclerosis of the large vessels at the base, and atheromata could be seen extending along the large vessels. There was clotted blood beneath the arachnoid over the inferior surface of the right temporal lobe and in part of the basilar cistern. There was a large defect, measuring 5 × 3 × 2 cm., in the anterior portion of the right temporal lobe, through which a large encapsulated clot had apparently been extruded. Coronal sections disclosed a hemorrhagic cavity which the clot had occupied. Dorsal to this was a fresh hemorrhage which extended medially over the putamen and pushed the head of the caudate nucleus medially. More caudally, the hemorrhage was confined chiefly to the Sylvian fissure. Dissection revealed a true saccular dilatation of the middle cerebral artery on the right side. No actual rupture was found.

Histologic study of the sections of the brain revealed subarachnoid hemorrhage with leucocytic infiltration, mainly polymorphonuclear cells and lymphocytes. Hemosiderin was scattered here and there. The pial vessels were moderately thickened. There was evidence of toxic ganglion cell disease and cell loss in the cerebral cortex.

CASE 3.—E. M.; No. DH 1763.

History.—The patient, a 58-year-old white married woman, known to be hypertensive for six years, was admitted to the Ashland State Hospital in Ashland, Pa., on July 1, 1951, in a semiconscious condition. She had attended a shooting match that afternoon and seemed to be very excited, when she suddenly complained of severe pain in the back of the head and a short time later became unconscious. Three convulsions followed that evening, each convulsion lasting about 30 seconds. She complained of pain over the left parietal region. There was papilledema of the right nerve head and a small flame-shaped hemorrhage above the disc. The left optic disc was well defined. The retinal vessels showed arteriosclerosis. The patient remained in a semiconscious state from the onset of her illness. Her general physical condition, however, appeared to be satisfactory. She was transferred to the neurosurgical service of the Jefferson Hospital on July 6, five days after onset of her symptoms.

Neurologic Examination.—On admission the patient was stuporous and reacted to painful stimuli. The pupils were equal. There was a small, old hemorrhage in O. D.; left central facial weakness; decreased movement of the left arm; marked nuchal rigidity, and a positive Kernig sign. The deep tendon reflexes could not be elicited.

Laboratory Studies.—The urine specimen was amber in color, with specific gravity of 1.024; there was a faint trace of albumin and 0.5% sugar. The blood count showed 91% hemoglobin, 4,650,000 red cells, and 10,400 white cells, with 81% neutrophiles, 18 lymphocytes, and 1 eosinophile. The blood urea nitrogen was 32.5 mg. per 100 cc. On lumbar puncture, the spinal fluid was found to be xanthochromic, containing a few red blood cells, and under a pressure of 230 mm. of water.

Course.—On July 7, six days after admission, the patient was noted to have left hemiparesis, and the weakness of the left side of the face became more marked. She became progressively worse, and during the ensuing week the weakness of the left arm and leg became complete. She went into deep stupor and died on July 16. During her period of hospitalization her blood pressure range was 130-180/80-120. Her temperature was persistently elevated, ranging from 101 to 103 F.

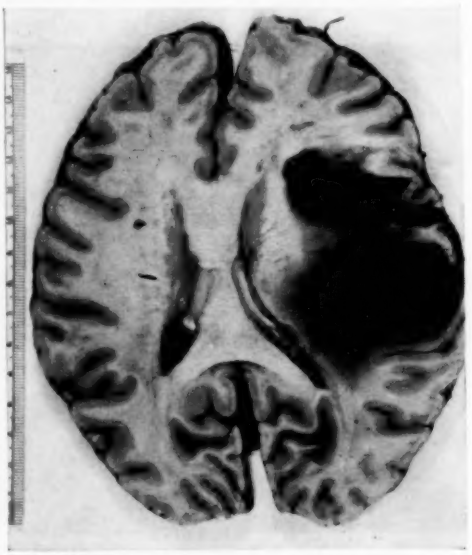


Fig. 2 (Case 3).—A large and recent hemorrhage in the right frontotemporal region resulting from rupture of middle cerebral artery aneurysm.

Autopsy.—Postmortem examination revealed severe congestion of the lungs, kidney, and spleen; arteriosclerosis of the kidney, and focal necrosis of the pancreas.

Examination of the brain revealed fresh blood spread diffusely over the dura, as well as a partially circumscribed blood clot, measuring 10.5 cm. in the anteroposterior diameter, over the right cerebral hemisphere in the region of the Rolandic

fissure (Fig. 2). The blood in the subarachnoid space tended to be localized over the right frontoparietal area in the region of the third frontal convolution, the precentral and postcentral gyri, and, most markedly, in the Sylvian fissure; but there was a smaller collection of subarachnoid blood over the first frontal convolution on the left side and a large amount of subarachnoid blood at the base of the brain. The gyri of the brain were flattened and edematous. The vessels of the circle of Willis contained atheromatous plaques, and there was an incomplete fusion of the two vertebral arteries. Dissection of the circle revealed a large saccular aneurysm, measuring 2×1 cm., on the right middle cerebral artery 1 cm. from its origin. There was a large fresh blood clot lying posterior to the aneurysm of the Sylvian fissure. The aneurysm had eroded a portion of the third frontal convolution and was partially embedded in it. Horizontal sections through the brain revealed a large recent intracerebral hemorrhage, beginning at the level of the head of the caudate nucleus on the right side and extending over the lateral edge of the internal capsule; behind this clot there was a larger clot, which involved some of the striations of the internal capsule closer to the surface of the brain. The hemorrhages extended over the Sylvian fissure. The right lateral ventricle was displaced to the left by the intracerebral hemorrhage. The ventricles did not contain blood.

CASE 4.—J. R.; No. PH 16360.

History.—The patient, a 45-year-old white married man, was well until April 15, 1953, when he had a violent sneezing and coughing spell while driving. Shortly thereafter he had excruciating headache, starting in the cervical and occipital regions and radiating anteriorly over the vertex to the frontal area. He drove his car to the side of the road, vomited, and rested for a time. He was later able to drive home, where he went to bed immediately. The headache initially was relieved by acetylsalicylic acid, but continued to increase in intensity and became associated with dizziness and vomiting. He was admitted to the Shamokin State Hospital on April 19, four days after the onset, where a history was obtained of a light blow to the head approximately two years previously, not associated with loss of consciousness. He had had occasional headaches, which he blamed on a sinus condition. He was a painter and a paper hanger by trade. Previously, he had done a great deal of drinking and continued to smoke heavily. Physical examination at the Shamokin State Hospital revealed the patient to be well oriented. His pupils were constricted and reacted sluggishly to light and in accommodation. The optic nerve heads were indistinct and suggestive of early papilledema. Neurologic examination revealed nuchal rigidity and generally overactive deep tendon reflexes. No localizing signs were present. A lumbar puncture, done immediately upon admission, revealed grossly bloody spinal fluid. Lumbar punctures on the third and fifth hospital days showed red cells and xanthochromia, respectively. Additional studies at that institution revealed an active duodenal ulcer. The patient was discharged on May 1, about two weeks after admission, with moderate nuchal rigidity and headache, which tended to be localized in the right frontal region.

He was admitted to the neurosurgical service in the Jefferson Hospital two weeks later, on May 16, having had no further symptoms except for continued dull headache, which was localized in the frontal region, and especially above the right eye.

Neurologic Examination.—On admission the findings were blurred disc margins on the right side, hyperactive reflexes on the right side, but no pathologic reflexes. There was an equivocal right facial weakness.

Laboratory Studies.—Urinalysis was negative. Complete blood count revealed 13.7 gm. of hemoglobin per 100 cc.; 4,570,000 red cells and 8,700 white cells, of which 54% were neutrophiles, 44% lymphocytes, and 2% eosinophiles. The blood Wassermann and Kahn reactions were negative. An x-ray of the skull revealed a densely calcified pineal gland, which was slightly displaced to the left. The x-ray of the chest was negative.

Course.—Right percutaneous arteriography was performed on the day of admission (Fig. 3). Shortly after the internal carotid artery was punctured, and before injection, a left facial weakness appeared. An aneurysm of a right middle cerebral artery was demonstrated. The patient immediately developed left hemiplegia. A stellate ganglion block was performed, without beneficial results. Lumbar puncture on the same day revealed a clear spinal fluid under pressure of 150 mm. of water. The left hemiplegia persisted. The patient became progressively more stuporous, and within one hour after the arteriography developed tonic convulsions involving both arms and the right leg occurring at three- to five-minute intervals. He died four hours after the arteriography.

On postmortem examination there was found a ruptured aneurysm, measuring 0.5 cm. in all diameters, at a distance of 3 cm. from the origin of the right middle cerebral artery. A massive hemorrhage into the white matter of the right temporofrontal region was present.

CASE 5.—C. D.; No. MH 9737.

History.—The patient, a 44-year-old white man, was admitted to the neurosurgical service of Dr. Rudolph Jaeger in the Jefferson Hospital on Dec. 27, 1949. He had been well until Thanksgiving

Fig. 3 (Case 4).—Right carotid arteriogram showing aneurysm of the middle cerebral artery.

Day, 1949, when he had sudden onset of severe right occiptal headache associated with vomiting. He could recognize friends and talk to them but forgot that he had seen them. This condition persisted for 12 days. Fourteen days after the onset, he noted transient numbness of the left side of the body and the left arm and leg, which persisted for two days, cleared completely, and did not return. He was hospitalized at the Providence Hospital in Washington, D. C., for a total of 21 days. During that time, he had repeated lumbar punctures and was told that he had a subarachnoid hemorrhage. Stiffness of the neck had been present since the onset and persisted for one week after discharge from the hospital. The patient had had pneumonia five times and empyema in 1946. He had had a carcinoma of the lip, which was removed surgically.

Examination.—Physical examination was normal except for a right thoracotomy scar and a scar in the lower outer corner of his mouth from the surgical removal of the carcinoma. Neurologic examination showed only hypesthesia to pinprick over the left forearm and hand.

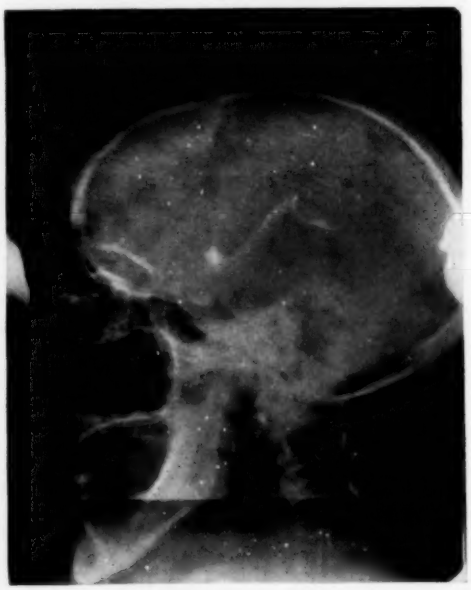
Laboratory Studies.—The urine and hemogram were normal.

Right carotid arteriography was performed (Fig. 4). This revealed an aneurysm of the middle cerebral artery at its bifurcation. On Jan. 4, 1950, a right frontal craniotomy was performed by Dr. Rudolph Jaeger. The dura over the temporal and frontal regions was thickened, due to a very thin subdural hematoma. The cortex was discolored by hemorrhage and was atropic. Between the frontal and temporal lobes there was felt an area of softening. About 1 in. (2.5 cm.) below the surface was a softened clot surrounding an aneurysm 2 cm. in diameter, attached to the main trunk of the middle cerebral artery just after the emergence of the temporal branch. At the attachment of the aneurysm there was found a smaller one, about 0.5 cm. in diameter, which came off the middle cerebral artery just before the main aneurysm. The aneurysm was excised. Following operation, the patient had slight weakness of the left side of the face and of the left hand grip.

CASE 6.—P. C.; No. PH 10048.

History.—The patient, a 50-year-old Negro woman, was admitted to the medical service in the Jefferson Hospital on Jan. 2, 1953, because of headaches and drowiness. Five days prior to admission, on Dec. 7, she noted the sudden onset of severe, violent, bitemporal headache associated with weakness of the right arm and leg. During the course of the next few days, she began to complain more of pain in the midback extending to the neck and to the back of the head; the headache eventually became localized in the frontal region over the right eye. There was some recession in weakness of the right arm and leg, until her admission to the hospital. In April, 1952, she was hospitalized because of menorrhagia. Physical

Fig. 4 (Case 5).—Right carotid arteriogram showing aneurysm of the middle cerebral artery.



examination on admission revealed a blood pressure of 190/100 and a temperature of 100 F. The patient had a Grade 2 apical systolic murmur.

Neurologic Examination.—This revealed a somnolent patient who was aroused with difficulty; nuchal rigidity and positive Kernig signs; suggestive dropping of the right corner of the mouth; mild weakness of the right arm and leg, and slightly more active deep tendon reflexes on the right side. The weakness and reflex inequality were more marked in the lower limb.

Laboratory Studies.—Urinalysis on admission revealed a faint trace of albumin; the blood count showed 72% hemoglobin; 3,630,000 red cells, and 6,200 white cells, of which 76% were neutrophiles, 32% lymphocytes, and 2% monocytes The Wassermann and Kahn reactions of the blood were negative. Blood urea nitrogen was 11.8 mg. per 100 cc., fasting blood sugar 105 mg., cholesterol 260 mg., and plasma protein 6.47 gm., per 100 cc., of which 3.77 gm. was albumin and 2.7 gm. was globulin. Lumbar puncture on admission revealed an xanthochromic fluid in which there were 5 cells per cubic millimeter and 31 mg. of protein per 100 cc. The Wassermann and colloidal gold reactions were normal. X-ray of the skull was normal. A routine eight-lead electroencephalogram revealed a slow-wave focus in the right frontoparietal area. The electrocardiogram failed to reveal evidence of myocardial damage.

Fig. 5 (Case 6).—Left carotid arteriogram showing aneurysm of left middle cerebral artery, verified at operation.

Course.—There was gradual improvement in the patient's condition. She became alert. Slight weakness of the right limbs persisted, but the facial weakness disappeared. She was treated conservatively, but on Jan. 10, eight days after admission, she suddenly became comatose. Lumbar puncture at this time revealed a bloody spinal fluid under a pressure of 280 mm. of water. The patient was then transferred to the neurosurgical service for arteriography. A left carotid arteriogram revealed an aneurysm measuring 0.5 cm. on the left middle cerebral artery, apparently 3 cm. from its origin (Fig. 5). In addition, the middle cerebral vessels were pushed upward and toward the midline, and there was a paucity of vessels in the temporal region. The anterior cerebral artery was not deviated from the midline. The impression was that of a middle cerebral aneurysm, and probably of a blood clot in the temporal lobe displacing the middle cerebral vessels medially and superiorly. Two hours after arteriography the patient developed a profound right hemiplegia and aphasia without loss of consciousness. During the next few days she remained partially aphasic, although the severe hemiplegia persisted. On Jan. 26, or 24 da s after admission, a left frontal craniotomy was performed by Dr. Rudolph Jaeger, who found a large subarachnoid hematoma, about ½ in. thick, covering the frontal, temporal, and part of the parietal lobes. The tip of the left temporal lobe was softened; it was opened, and a clot of about 30 cc. of blood was found within it. This led down to a very much enlarged middle cerebral artery. On the middle cerebral artery was an irregularly shaped aneurysm with a base about 3 mm. in diameter. It was possible to close the neck of the aneurysm with an aluminum clip and yet leave the middle cerebral circulation intact. The convalescence was stormy and was complicated by an ulcer on the right leg, which required surgical débridement and skin grafting. The patient was discharged from the hospital on March 30, with severe aphasia and a complete right hemiplegia. Throughout the course of her hospitalization, her blood pressure showed a marked tendency to variation, ranging between 140 and 220 systolic and 70 and 110 diastolic.

CASE 7.—J. R.; No. GH 3509.

History.—This 38-year-old white unmarried saleswoman was admitted to the neurologic service of the Jefferson Hospital on Sept. 1, 1943, in coma. She was well until April, 1943, five months before admission, when she had a sore throat, a temperature of 101 to 102 F, and difficulty in swallowing. Her family physician reported that the patient had acute rheumatic fever at that time. The patient's sister reported that since April, 1943, she had been unable to work, appeared exhausted, slept a great deal, and complained of headaches in the occipital region, but more frequently in the frontal and supraorbital areas. She also complained of dizziness. During the few months prior to her

admission her speech was normal most of the time, but on infrequent occassions it was slurred and resembled a Southern drawl. She was also noted to have some difficulty in picking out the proper word. On the morning of her admission to the hospital, without premonitory symptoms, she was found unconscious in bed and could not be aroused. The past medical history revealed influenza and pneumonia at the age of 12 years and an appendectomy at 17 years of age. She had had a 20 to 24 lb. weight loss since April, 1943, and had had no menses since that time.

Physical Examination.—The findings were petechiae in the left lower conjunctival sac; enlargement of the heart to the anterior axillary line, and systolic and diastolic murmurs at the apex. The lungs were clear, and the abdomen was normal.

Neurologic Examination.—The patient was comatose with stertorous breathing. The right pupil was larger than the left and was fixed to light; the left pupil reacted slightly to light. The right corneal reflex was absent; the left was decreased. There was papilledema of 3 to 4 D. with hemorrhage in the right eye and papilledema of 2 D. in the left eye. A right internal rectus palsy and right central facial weakness were found. The limbs were spastic, with a bilateral Babinski sign and tonic tremors of all the limbs, more marked on the right side. There was no nuchal rigidity or Kernig sign.

Laboratory Studies.—Urinalysis showed 2+ albumin and many pus cells. The hemoglobin was 54% with 3,090,000 red blood cells and 6,800 white blood cells, of which 85% were polymorphonuclear cells, 17% lymphocytes, and 8% monocytes. The Wassermann and Kahn reactions of the blood were negative. Culture of the blood failed to reveal a growth in 48 hours. The nonprotein nitrogen was 25 mg. per 100 cc.; blood sugar 162 mg. per 100 cc., and the CO_2-combining power was 61.4 vol.%. The spinal fluid was under an initial pressure of 230 mm. of water. It was cloudy and blood-tinged. Culture of the spinal fluid failed to reveal any growth in 48 to 72 hours. Culture of the urine revealed Pseudomonas aeruginosa (B. pyocyaneus). Roentgenogram of the skull was negative.

Course.—The patient remained comatose during the period of hospitalization. Neurologic examination was unchanged save for increase in spasticity of the limbs two days before death. The temperature, pulse rate, and respiration rate continued to be elevated, ranging from 101-104 F, 120-160 pulsations a minute, and 26-40 respirations a minute. The blood pressure was not elevated. Death occurred on the seventh day of her illness.

Postmortem Examination.—An old rheumatic endocarditis involved the mitral leaflets, with superimposed subacute bacterial endocarditis, pulmonary congestion, and edema. There was an infarction of the spleen.

The brain revealed subarachnoid hemorrhage over both frontal lobes. Over the right frontal lobe, involving the second and third frontal gyri and the inferior portion of the precentral gyrus, was an irregular, jagged laceration in the cortex measuring 4×2 cm., from which extruded a well-fixed blood clot. No aneurysmal dilatation was apparent in the circle of Willis, but in the right Sylvian fissure, along one of the branches of the middle cerebral artery, was a small orange-yellow mass loosely applied to the vessel. When this was removed, there was revealed an open sac about

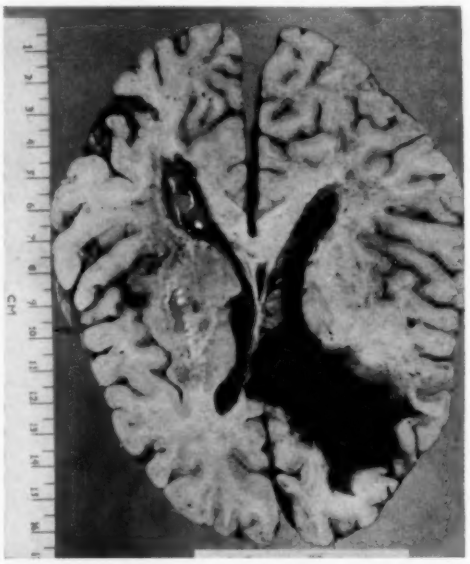


Fig. 6 (Case 7).—A large left frontal hemorrhage due to a ruptured middle cerebral artery aneurysm.

3 mm. in diameter; the side of the vessel was softened. Horizontal sections of the brain revealed a hemorrhage, measuring 3×5 cm., in the right frontal lobe. The ventricular system was displaced to the left (Fig. 6).

The meninges contained a scattering of red blood cells and a number of phagocytic cells containing hemosiderin. In all of the regions studied, but more marked in the gray matter, were necrotic areas containing massed leucocytic cells, mainly lymphocytes and polymorphonuclears. These areas varied considerably in size and were occasionally associated with slight to moderate hemorrhages. Some of these areas were about blood vessels, particularly capillaries.

CASE 8.—M. C.; No. U 8397.

History.—The patient, a 56-year-old Negro woman, was brought in coma to the medical service of the Jefferson Hospital on Dec. 19, 1947. The following information was obtained from her husband: The patient was well until 3 o'clock on the day of admission. She had done her housework and was chatting with neighbors, when, without warning, she fell backward into a chair and became unconscious. Five minutes after the onset of unconsciousness her right arm began to twitch, as though she were having a chill. She had been known to have high blood pressure for one year. In July, 1947, five months before the present illness, the patient suffered an episode of unconsciousness but had no paralysis. On regaining consciousness at that time, she complained of loss of sight in her right eye. Except for the loss of vision, she was well in the interim.

Physical Examination.—Respirations were irregular; otherwise the heart, lungs, and abdomen were normal. The right pupil was pinpoint and did not respond to light; the left pupil reacted normally. In the left fundus there were several large retinal hemorrhages; the right fundus was not visualized. She had flaccid paralysis involving all her limbs and a positive Babinski sign bilaterally.

Laboratory Studies.—The hemoglobin was 11.5 gm. per 100 cc.; red blood cells were 4,100,000, and the white blood cells were 10,500, of which 78% were neutrophiles, 21% lymphocytes, and 1% monocytes. Urinalysis showed 3+ albumin and casts. The nonprotein nitrogen was 52 mg., and sugar 133 mg., per 100 cc., and the CO_2-combining power was 48 vol.%. The spinal fluid was under pressure of 230 mm. water and was bloody. The Wassermann reaction of the spinal fluid was negative.

Course.—The patient remained comatose during the entire period of hospitalization. The paralysis of her limbs persisted; her extremities remained flaccid until her death, six days after admission to the hospital. Two additional lumbar punctures revealed bloody spinal fluid under increased pressure. The patient's blood pressure ranged from 160-210/110-130.

Postmortem Examination.—There were pulmonary congestion, edema, focal atelectasis, and emphysema. The brain showed a massive basilar hemorrhage extending into the left Sylvian fissure. The hemorrhage undermined the left hippocampal gyrus, which existed only as a shell of necrotic tissue. The vessels of the circle of Willis showed atheromatous plaques. The end of the middle cerebral artery approximating the left internal carotid artery was frayed and blood-stained, and may have ruptured, producing hemorrhage. At the ruptured end of the posterior communicating artery was a large dilatation of the vessel wall, measuring 1 cm. in all diameters; this, too, was open. The opening corresponded with the torn end of the middle cerebral artery. Horizontal sections of the cerebrum revealed only subarachnoid hemorrhage of the left Sylvian fissure.

Microscopic study of the subarachnoid hemorrhage revealed it to be recent in origin. The arteries in the Sylvian fissure were markedly sclerotic. The smaller arteries and arterioles were hyalinized and had undergone coagulation necrosis. Sections of the caudate nucleus and putamen revealed an old, small vascular softening with a few gitter cells and scarring. Sections of the optic nerves revealed subarachnoid hemorrhage about these structures. The nerves themselves were normal.

CASE 9.—C. H. H.; No. NH 11107.

History.—The patient, a 57-year-old white married man, was admitted to the medical service of the Jefferson Hospital in a comatose state on Jan. 17, 1951. His son states that his father had been drinking wine an hour earlier, when, without apparent warning, he fell backward, his right arm began to shake, his right hand jerked spasmodically, and his eyes rolled up in his head. The past medical history disclosed that three years previously the patient was noted to have a "mushy" speech, with difficulty in expressing himself. When he was unable to speak his thoughts, he blurted out expletives which could not be clearly understood. He had no difficulty in understanding. The patient had been drinking alcohol to excess for many years, and, although his family attributed the speech disorder to prolonged drinking, a friend stated that the patient had choked while fighting and had had difficulty in expression since then.

Neurologic Examination.—The patient was comatose; he was able to withdraw from painful stimuli. The fundi were normal except for retinal arteriosclerosis. The head and eyes were turned to the right. He had a left central facial weakness, and the left extremities were flaccid, while there was marked spasticity of his right extremities. A grasp reflex was present in the right hand. The deep tendon reflexes in the right upper limb were hyperactive, while those in the left upper extremity were decreased. The leg reflexes were decreased bilaterally; no pathological reflexes were elicited. He had nuchal rigidity and a bilaterally positive Kernig sign.

Laboratory Studies.—The urine was brown in color; the specific gravity was 1.019; there was 3+ albumin, but tests for sugar were negative; microscopic examination revealed 15-20 white blood cells and 20-30 red blood cells. The blood count revealed 117% hemoglobin, 5,550,000 red cells and 12,600 white cells. The nonprotein nitrogen was 22.2 mg., the fasting blood sugar was 161 mg., per 100 cc., and the CO_2-combining power was

40.4 vol.%. Lumbar puncture on Jan. 17 revealed a bloody spinal fluid under pressure of 60 mm. of water. Another lumbar puncture was performed on Feb. 12; at that time the spinal fluid was slightly cloudy, but it was colorless. X-ray studies of the chest disclosed pleural thickening over both apices with some increase in the pulmonary markings in the upper lobes, particularly on the left. The patient did not regain consciousness. His course was progressively downhill, and he died on Feb. 18. During his period of hospitalization his blood pressure ranged from 140-210/100-140.

Postmortem Examination.—Autopsy revealed severe congestion and edema of the lungs with terminal pneumonia; dilatation of the heart; arteriosclerosis of the kidneys, and venous congestion of the viscera. Subarachnoid blood was scattered over both cerebral hemispheres; there was a tendency for the blood to collect in the posterior portion of the right frontal lobe.

The brain showed a large area of destruction involving chiefly the second and third left frontal convolutions, beginning 1 cm. posterior to the frontal pole and extending posteriorly for a distance of 5 cm. The lateral half of the left frontal lobe had been destroyed, the lesion involving Broca's area, the inferior portion of the precentral gyrus, and the inferior portions of Areas 6 and 8. On the right side of the brain, the temporal pole was softened. The circle of Willis had many atheromatous plaques. When it was dissected, a small ruptured aneurysm was found on the right side about 1 cm. from the origin of the middle cerebral artery. Horizontal sections through the cerebrum showed old softening and loss of tissue in the left frontal lobe. On the right side there was fresh intracerebral hemorrhage, beginning at the upper medial side of the frontal lobe 3.5 cm. from the frontal pole and extending laterally through the white matter. The cortical arteries showed advanced arteriosclerosis.

CASE 10.—L. D.; No. JH 11002.

History.—The patient, a 49-year-old married woman, was admitted to the neurologic service of the Jefferson Hospital on Feb. 7, 1947, because of seizures, which had begun three years earlier and had increased in severity shortly before her entrance into the hospital. At the onset in 1944, three years previously, the attacks, which occurred at frequent intervals, began with a sensation of water trickling down the right side of her head, face, and neck. This sensation was followed by twitching of the right side of the mouth and right arm. She retained consciousness during the attacks, which varied in duration from several seconds to several minutes. At times, either accompanying an attack or independent of it, she perceived an unpleasant putrid odor, complained of a bad taste "like pus from a tooth," and smacked her lips. During three attacks earlier in her illness, and during a group of seven seizures which occurred in a 24-hour period three weeks before entering the hospital, she lost consciousness. The seizures associated with loss of consciousness were similar to the others, but they also included head and eye deviation to the left after consciousness was lost, as well as a spread of the motor twitching to involve the entire body, frothing at the mouth, and biting of the tongue. Unconsciousness persisted for 15 minutes, and the patient then slept for several hours. Following the succession of seizures shortly before her admission, the patient began to complain of blurred vision, which was present when she entered the hospital. She had had intermittent right-sided headaches, beginning in 1942. These persisted for three months and did not recur later in her illness. Her general health had been good. In 1945, her menses became irregular, with prolonged periods and spotting. For an indefinite period of time she had noted pain and blanching of her hands when they were exposed to the cold. Physical examination revealed no abnormalities of the heart, lungs, or abdomen. The blood pressure ranged from 90-130/50-70. Neurologic examination was normal.

Laboratory Studies.—Urinalysis was negative. The blood count showed a hemoglobin of 71%, 3,600,000 red cells, and 5,000 white cells. The Wassermann and Kahn reactions of the blood were negative. The blood urea nitrogen was 5.4 mg. per 100 cc., and the urea clearance 130% of normal. The total cholesterol was 205 mg., free cholesterol 24.6 mg., and the cholesterol esters 180.4 mg., per 100 cc. Spinal fluid examination revealed an absence of cells, a total protein of 24 mg. per 100 cc., a negative Wassermann reaction, and a colloidal gold curve of 0000000000. A 16-lead electroencephalogram revealed no abnormalities. Visual field studies were normal, and the visual acuity was 20/15 bilaterally. Roentgenograms of the chest were negative. Roentgenograms of the skull revealed a linear calcification lying in the region of the right temporal horn above and to the right of the sella turcica. An encephalogram showed a slight but definite shift of the ventricular system to the left and also a suggestion of a flattening of the lateral wall of the left ventricle. It was thought that the findings were quite conclusive of a tumor in the right temporal region associated with calcification.

Course and Operation.—Arteriogram revealed an aneurysm of the intracranial portion of the right internal carotid artery. Dr. Rudolph Jaeger performed a right cerebral craniotomy on March 10, about five weeks after admission. An aneurysm of the right middle cerebral artery was disclosed. The aneurysm filled the middle fossa at the point

of the temporal lobe, measuring about 1½ in. in diameter. The middle cerebral artery forked into two branches about ½ in. beyond the anterior cerebral artery. One branch penetrated the aneurysm and emerged from it about 1 in. from its point of origin. The second branch was tightly adherent to the aneurysm. A clip was placed on the middle cerebral artery just before it forked and ½ in. from the anterior cerebral artery. The branch overlying the mass was clipped, and both were cut between the aneurysm and the clips (Fig. 7). After operation there was complete paralysis of the left side of the face and left arm and leg; the leg was less severely involved than the arm. Five days after operation, the patient became cyanotic, breathing was laborious, and she died.

An autopsy was not obtained. Sections of the operative specimen were studied. Sections of the aneurysm revealed the wall to consist of intima and adventitia. The intima was markedly proliferated and degenerated, with atherosclerosis and calcification. The one edge of the specimen was a small section of media and elastica; this probably represented the parent vessel.

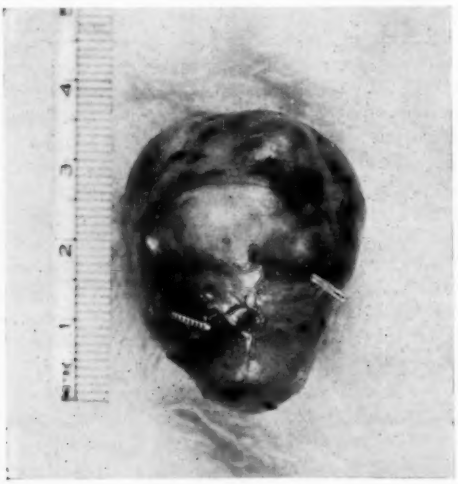


Fig. 7 (Case 10).—A large middle cerebral artery aneurysm removed at operation.

CASE 11.—W. K., No. MH 11311.

History.—The patient, a 31-year-old married white graduate student, was admitted to the Jefferson Hospital on Jan. 27, 1950, because of headaches and seizures of nine days' duration, weakness of the left arm and face, and double vision of two days' duration. Two weeks before entering the hospital he had an upper respiratory infection, from which he recovered save for a purulent nasal discharge and a slight productive cough. Nine days before admission, while taking a final examination, he had a buzzing sensation in the back of his neck, which spread upward, and he suddenly blacked out and became stiff all over. He fell to the floor and remained unconscious for one to two minutes. He had no clonic movements of the limbs while he was unconscious. Immediately following the seizure he complained of severe headache associated with photophobia. At first the headache was generalized, but later it tended to be severer in the suboccipital and frontal regions. About one hour after the loss of consciousness he had another episode, characterized by the rolling back of the eyes, followed by a generalized tonic seizure without tongue biting or sphincteric disturbances. He was unconscious for about one minute. There were no further seizures. He had no fever at that time and was able to be up and about, although he was continually sleepy. He remained in the University infirmary but did not seem critically ill. Five days later it was noted that the patient was running a daily elevation of temperature, and he was given penicillin and chlortetracycline (Aureomycin). The next day the headache became severer and changed in location to the right temporal area. The change in the location of the headache was associated with diplopia and weakness of the left arm and leg, more marked in the arm, and with weakness of the left side of the face. He had had severe headaches for years, but they had increased in severity during the past six months. They were concentrated in his eyes but at times became generalized. The past medical history revealed infection with malaria while in the Army, in 1943. Physical examination was within normal limits.

Neurologic Examination.—This revealed early choked disc; left homonymous hemianopsia; left lower facial weakness with paralysis of the left arm and pronounced weakness of the left leg; faster tendon reflexes on the left with a positive left Babinski sign; loss of position sense in the left thumb and great toe; loss of vibration sense in the left arm and leg, and decreased pain sensation over the left extremities and left side of the trunk.

Laboratory Studies.—Urinalysis was normal. The blood count revealed 84% hemoglobin, 4,500,000 red cells, and 19,500 white cells, of which 64% were neutrophiles, 34% lymphocytes, and 2% eosinophiles. The Wassermann and Kahn reactions of the serum were negative. On lumbar puncture the initial pressure was 260 mm. of water. The spinal fluid was xanthochromic; there were 7 cells per cubic millimeter, 54 mg. of total protein per 100 cc., a negative Wassermann reaction, and a colloidal gold reaction of 0000000000. X-ray examinations of the chest and skull were negative. The left antrum appeared cloudy.

A craniotomy was performed by Dr. Rudolph Jaeger on Jan. 30, three days after admission. When the right frontal, temporal, and parietal lobes were exposed, the brain was found under considerable tension. Despite careful exploration, no other abnormalities were disclosed. A section of cortex removed during the operation was found to be normal on histologic study. During the period following his operation the patient had several seizures, and on Feb. 12, or 16 days after admission, he lapsed into a coma and died.

Postmortem Examination. — Autopsy revealed severe congestion and edema with terminal pneumonia in the right lung and congestion of the spleen, liver, kidneys, and adrenals. Examination of the brain revealed a large, firm extradural clot measuring 9.5×7.5 cm. and a clot 6 cm. in diameter attached to the subdural surface. There was distortion

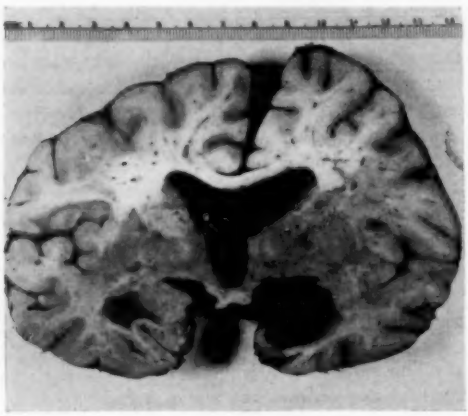


Fig. 8 (Case 11).—Encapsulated hemorrhage in the right temporal lobe, erupting into the ventricles, associated with a middle cerebral artery aneurysm in the area of hemorrhage.

of the hemispheres, the right being pushed across the midline. At the base of the brain there was a blood clot in the right temporal lobe measuring 2 cm. in diameter and diffuse subarachnoid hemorrhage. Coronal sections of the cerebrum revealed an area of discoloration and a blood clot beginning in the right second frontal convolution and extending backward to the posterior edge of the striate body (Fig. 8). There was a large clot in the right lateral ventricle and the third ventricle. In the right temporal lobe there was a fresh clot which appeared encapsulated. At the level of the pulvinar there was an area of softening, which was limited to the white matter. Microscopic study of the blood clot from the temporal lobe revealed a well-formed clot containing a medium-sized blood vessel; the blood vessel wall in one portion was very thin and had lost its media.

CASE 12.—P. S.; No. LH 6093.

History.—The patient, a 51-year-old white man, was admitted in a comatose state to the neurologic service of the Jefferson Hospital on Oct. 13, 1948. He was transferred from the Wilkes-Barre General Hospital, and the only information available was obtained from the record sent by the referring institution. The patient had entered there 18 days previously, on Sept. 25, 1948, having been brought by the police, who had found him wandering the streets in a confused state. An informant stated that the patient had had episodes of wandering previously but that he had been perfectly rational immediately preceding the incident. He had had severe headaches for a considerable period. He had drunk alcohol excessively. On admission to the Wilkes-Barre General Hospital, he was confused but responded to commands.

Physical Examination.—There was drooping of the left eyelid with enlargement of the left pupil, which did not respond to light; he could move his extremities and the deep tendon reflexes were overactive. The blood pressure ranged between 180/70, on admission, and 150/88, during his hospital stay. Roentgenograms of the chest and skull were negative. Lumbar puncture was performed; during the procedure the patient had several convulsive seizures. The spinal fluid was xanthochromic and under 400 mm. of pressure and contained red blood cells; the remainder of the spinal fluid studies were normal. Urinalysis was negative. The blood count showed 3,700,000 red cells and a normal white cell count. The Wassermann and Kahn reactions of the blood were negative. The patient did well during the first two days of his hospital stay; he then became drowsy, was difficult to arouse and uncooperative, and failed to speak. He was found to have difficulty in moving his right arm, and the next day had a flaccid paralysis of the right arm and leg. An eye consultant found bilateral papilledema. Neurologic examination 11 days after entrance revealed a stuporous state, right hemiparesis, and incontinence of the bowel and bladder. The patient was transferred to the Jefferson Hospital with the diagnosis of an intracranial space-taking lesion, possibly a cerebral aneurysm. Physical examination revealed stertorous breathing with decreased expansion of the lungs, but the lungs were clear to auscultation. Examination of the heart showed a marked precardial thrust; the point of maximum impulse was at the xiphoid process; there was a basal systolic murmur; the rhythm was normal.

Neurologic Examination.—This revealed a stuporous patient; marked nuchal rigidity; dilation of the pupils, which were fixed to light, the left pupil being 1 to 2 mm. larger than the right; questionable ptosis of the left eyelid; papilledema of 5-6 D. with

hemorrhages in the right eye and of 3-4 D. in the left eye; flaccid hemiplegia; absence of deep and superficial reflexes on the right side, and no response to plantar stimulation on the right side; active deep tendon reflexes on the left side, and response to pinprick on the left arm but not on the right.

Laboratory Studies.—Urinalysis revealed 2+ albumin. The blood count showed 97% hemoglobin; 5,400,000 red cells, and 17,600 white cells, of which 82% were neutrophiles, 11% lymphocytes, and 7% monocytes. The blood urea nitrogen was 25.6 mg., and creatinine 1.9 mg., per 100 cc. The patient died 48 hours after his entrance into the hospital.

Fig. 9 (Case 12).—Dissection of the circle of Willis showing the aneurysm of the right middle cerebral artery.

Postmortem Examination.—Findings were severe atherosclerosis of the coronary arteries with partial occlusion of the left anterior descending branch; myocardial fibrosis of the left ventricular septum and left ventricle; generalized arteriosclerosis, and congestion of the lungs, spleen, kidneys, and liver. The brain showed many small subarachnoid hemorrhages over the frontal lobe, the right occipital lobe, and the right cerebellar hemisphere. There was an increase in the markings around the cerebellar tonsils. The vessels of the circle of Willis were sclerotic. There was a small saccular aneurysm at the branching of the superior cerebellar artery on the right side and a larger saccular aneurysm, measuring 0.8 cm., at the branching of the left middle cerebral from the left internal carotid artery. The aneurysm was attached to the middle cerebral artery by a short stalk (Fig. 9). There was a small depression in the left uncus where the aneurysm lay. Coronal sections revealed fresh blood from the subarachnoid space in the left Sylvian fissure. There was a poorly circumscribed, pinkish-gray lesion involving the left second frontal convolution, beginning at the level of the optic chiasm and extending back to the middle of the third ventricle. The entire brain, including the cerebellum, was congested, and there was fresh blood in the occipital poles of the lateral ventricles with some staining of the white matter at the tip.

Microscopic studies revealed the meningeal vessels to be thickened. There was a small amount of subarachnoid blood overlying the cortex. Several areas in the cortex had been destroyed and replaced by gitter cells and gemästete astrocytes, with many young blood vessels growing in. There was an increase in the perivascular and pericellular spaces. Many of the ganglion cells were shrunken and pyknotic. In sections through the lateral ventricle there were small areas of extravasated red blood cells surrounding the ventricle.

ANALYSIS OF SYMPTOMS

For purposes of correlation of the findings in all the reported cases of aneurysm of the middle cerebral artery, a careful survey was made of the literature. There were located 129 cases, but of these only 75 were found to be sufficiently complete to warrant inclusion for study. To them have been added the 12 cases here reported.

Age.—In the cases reported in the literature the majority of patients fell within 20 to 50 years of age (44 cases). The distribution of the reported cases was as follows: under 10 years of age, 3; 10 to 19 years, 8; 20 to 29 years, 18; 30 to 39 years, 11; 40 to 49 years, 15; 50 to 59 years, 7; 60 to 69 years, 8; 70 to 79 years, 1; 80 to 89 years, 1, with 3 not recorded. It was not possible to determine the age of onset of the initial symptoms for lack of information in the reported cases.

Of the cases reported in our series of 12 patients, 2 fell in the group of 30 to 39 years, 4 in the group of 40 to 49 years, and 6 in the age group of 50 to 59 years. The average age on admission to the hospital was 48.3 years.

Sex.—In the cases recorded in the literature men outnumbered women in a ratio of 44:30. In our series six patients were men and six women.

Duration of Symptoms.—Among 40 patients for whom information was available, the symptoms prior to rupture of the aneurysm were of less than one week's duration. In other instances the duration was as follows: 1 week to 1 month, eight cases; 1 to 2 months, six cases; 2 to 3 months, three cases; 3 to 6 months, one case; 6 to 12 months, two cases. In 15 patients the symptoms varied from 1 to 15 years, and 3 patients had had symptoms for 15 to 20 years.

No reliable data were available for the patients reported in this series.

Symptoms Prior to Acute Episode.—Among the patients recorded in the literature, 38, or slightly more than half the group, had no symptoms before admission to the hospital. Of the remainder, generalized headache was recorded in 16 instances and focal headache in 7; in the latter group it was found on the side of the aneurysm in 6 instances. Facial pain was present with the headache in four instances. Seizures were reported in seven cases, and of these, three were focal. Unconsciousness was found in three cases. Transient weakness appeared as hemiplegia in two instances and as loss of power of the legs in another. Unilateral impairment of vision was reported in one case, and bilateral impairment in another. Unilateral ptosis of the eyelid was found in only one case; unilateral tinnitus, in one case, and vertigo, in two cases.

In our series headache was the commonest symptom prior to the onset of the acute episode, varying in duration from five days to several years. Seizures were reported in only one instance (Case 12); these were right sensorimotor seizures associated with an unrupted aneurysm of the left middle cerebral artery. Weakness was found in three cases. In one instance (Case 8) it was transient. In another (Case 12) the patient reported inability to move the right limbs 18 days before admission to the hospital. In a third case (Case 6) there was sudden onset of weakness of the right arm and leg. Aphasia was recorded in two cases: One (Case 9) had had difficulty in expression for a period of three years; in the other (Case 6) there was difficulty in selecting words five months prior to admission. Unilateral loss of vision was reported in one instance (Case 8). Blurring of vision was recorded in one case (Case 10). Drooping of the eyelid was reported in one instance (Case 10).

In our series, the only symptom of significance before the acute onset was headache, which was present in six instances. Its duration varied widely, and its characteristics regarding location, type, or occurrence were not clearly defined. The only symptoms of localizing value were uncinate seizures in one case and expressive aphasia in another.

Symptoms at Onset of Acute Episode

Among 37 patients reported in the literature, loss of consciousness was the presenting symptom, associated in all instances with rupture of the aneurysm. Nineteen patients had headache, which was unilateral in 7 instances. Convulsions were reported in 24 patients with ruptured aneurysm: generalized in 15 and focal in 9. Convulsions were reported in only three instances of unruptured aneurysm. Weakness or paralysis of the limbs and/or face was recorded in 17 patients and aphasia in 3 cases. Other symptoms at the time of the acute episode were as follows: diplopia (two cases), blurred vision (two cases), oculomotor weakness (four cases), astereognosis (one case), and numbness of the limbs (three cases).

In our cases, 11 patients entered the hospital at the onset of subarachnoid or cerebral hemorrhage. In one instance (Case 10) the aneurysm was unruptured, and in this instance there was a progressive history of five years' duration, seizures for three years, and blurring of vision of three weeks' duration. The onset in 11 cases was with loss of consciousness or with severe headache. Generalized seizures were present in three instances, and in one (Case 8) focal seizures of the right arm were encountered. Weakness

or paralysis was found in five cases. This consisted of weakness of the face, arm, and leg in one instance; of the arm and leg alone in two patients; of one leg in one patient, and of all the limbs in another. Transient numbness of the arm and leg was found in one instance (Case 5). Headache was difficult to evaluate at the time of onset because of the frequent impairment of consciousness. Diplopia was noted in one instance. Among the contributory factors were a history of hypertension (four cases), rheumatic heart disease (one case), and coronary artery disease (one case).

The symptoms at the onset of the acute episode were usually apoplectiform, with loss of consciousness (eight cases), convulsions (four cases), weakness or paralysis (five cases), and transient sensory disturbances (one case). It is noteworthy that the weakness or paralysis was not confined to the anatomical distribution of the middle cerebral artery.

Examination in Acute Episode

Neurologic examination of the reported cases revealed a variety of findings. Abnormalities of the fundi were noted in 17 patients: swelling of the nerve heads (10 cases), retinal hemorrhage (4 cases), retinal arteriosclerosis (1 case), and pallor of the optic discs (2 cases). Visual field defects were found in six patients: homonymous hemianopsia (three cases), nasal anopsia on the side of the aneurysm (one case), complete loss of vision (one case), and bitemporal hemianopsia (one case). Pupillary abnormalities were noted in 16 instances: unilateral dilatation ipsilaterally (13 cases), bilateral dilatation (2 cases), and contracted pupil (1 case). Extraocular muscle weakness was found in nine cases; oculomotor palsy (eight cases), and abducens nerve palsy (one case). The corneal reflex was absent on the side of the aneurysm in one case. Facial weakness was present in 17 cases: on the side of the aneurysm in 5 cases and on the side opposite the aneurysm in 12 cases. Weakness of one side of the tongue was present in two instances. Thirty-five patients had weakness or paralysis of the extremities. The deep tendon reflexes were increased in seven and decreased in five patients. The Babinski sign was noted in 19 instances. Sensory impairment was rare. There was contralateral impairment of sensation in one case and astereognosis in the opposite arm in one case. Aphasia or loss of speech was noted in nine cases.

Personal Cases.—Neurologic examination in our 12 cases revealed papilledema (5 cases) and blurred discs (1 case). Hypertensive retinitis was noted (one case), retinal arteriosclerosis (three cases), and retinal hemorrhage (one case). Homonymous hemianopsia was present in two cases. Pupillary abnormalities were noted in three cases: In two of these the ipsilateral pupil was dilated and fixed. In one instance a small fixed pupil was found on the side opposite the aneurysm. Extraocular movements were impaired in three cases, always on the side of the aneurysm. In one case (Case 12) there was ptosis of the eyelid. In two instances (Cases 1 and 7) there was unilateral abducens palsy, of which one was transient. The corneal reflex was absent in one case (Case 4) on the side of the aneurysm. Central facial weakness was found in six cases. Paralysis or weakness of the extremities was present in nine cases: hemiplegia or hemiparesis, four cases; monoparesis, two cases, involving the arm in one and the leg in the other; flaccid quadriplegia of all limbs, two cases, and spastic quadriplegia one case. There was no evidence of limb, weakness in three cases. The deep tendon reflexes were increased in one instance and decreased in four cases. A unilateral Babinski sign was present in one case and a bilateral Babinski sign in two cases. Although there was evidence of recent subarachnoid hemorrhage in 11 cases, signs of meningeal irritation were present in only 8 instances. Sensation was impaired in three instances: In one (Case 12) there was unilateral impairment of pain sensation on the side opposite the aneurysm, and in the other (Case

11) there was unilateral impairment of pain, position, and vibration sensations on the side opposite the aneurysm. In the third instance (Case 5) pinprick was less well perceived in one arm.

The neurologic pattern at the time of admission of patients to the hospital was quite consistent. In nine patients there was some degree of pyramidal tract involvement—monoparesis, hemiparesis, or hemiplegia, usually with central facial weakness. Beyond this there were no consistent findings except for the fundus changes, which revealed papilledema, blurred discs, hypertensive retinitis, retinal arteriosclerosis, and retinal hemorrhage. Homonymous hemianopsia served as a localizing sign in two instances. In all cases there was clinical evidence of subarachnoid hemorrhage consistent with the rupture of the aneurysm.

Laboratory Studies

In the cases recorded in the literature, the cerebrospinal fluid was bloody in 26 instances, xanthochromic in 6, and clear in 3; the appearance of the spinal fluid was not recorded in 40 cases. In those instances in which spinal fluid pressure was recorded, the pressure tended to be elevated. The spinal fluid pressure was low in one case; in the range of 50 to 90 mm. of water in four; 100 to 190 mm. in one; 200 to 290 mm. in six; 300 to 400 mm. in two, and increased in three.

Roentgenograms disclosed calcification in the temporal region in two instances, pineal shift in one, and expansion of the sella turcica with thinning of the floor in one case. A pneumogram revealed a ventricular shift in one case.

In our personal cases, the cerebrospinal fluid was bloody in seven instances, xanthochromic in four, and clear and colorless in one. In seven instances the spinal fluid pressure was increased, ranging from 230 to 400 mm. Electroencephalographic studies were performed on three patients; in two they were found to be normal. The third (Case 6) revealed a slow-wave focus. Roentgenograms of the skull were negative in five patients; in one (Case 10) routine examination of the skull revealed a linear calcification in the temporal region. In another (Case 4) the pineal was shifted to the left. Arteriography was performed in five cases: In four it revealed an aneurysm of the middle cerebral artery; in the fifth the arteriogram was suggestive of an aneurysm of the internal carotid artery.

Operative and Autopsy Findings

Operative Cases.—Five of our patients were operated on. In one (Case 1) an aneurysm was found at the junction of the left middle cerebral and internal carotid arteries. The aneurysm, which had ruptured into the base of the left frontal lobe, appeared to arise from the left middle cerebral artery. In another (Case 4) there was a ruptured aneurysm of the right middle cerebral artery with hemorrhage into the brain substance. In Case 5 there were two aneurysms of the right middle cerebral artery; one had ruptured and was surrounded by clot. In Case 6 there was softening of the tip of the left temporal lobe associated with ruptured left middle cerebral artery aneurysm. In the last case in which surgical exploration was done the aneurysm was unruptured (Case 10). Here, an aneurysm, 1½ in. in diameter, filled the middle fossa at the tip of the temporal lobe.

Petit-Dutaillis and Pittman found 76 cases in the literature in which the patients were subjected to surgery. Of these, 66% were successfully treated, 25% died, and 9% survived, with disability. Practically all patients had had recent subarachnoid hemorrhage.

Autopsy Findings.—Of the 12 aneurysms of the middle cerebral artery here reported, 8 involved the right and 4 the left middle cerebral artery. Two of the aneurysms occurred at the junction of the middle cerebral with the internal carotid artery. Two occurred 1 cm. from the origin of the middle cerebral artery from the internal carotid artey. Two of the aneuysms were located at the tip of the temporal lobe; two were

found at the first branching of the middle cerebral artery, and the remaining four involved the middle cerebral artery in the Sylvian fissure. In one instance a small, unruptured aneurysm was found involving the right superior cerebellar artery, in addition to the left middle cerebral artery.

The aneurysms ranged in diameter from 3 mm. to more than 2 cm. There was one aneurysm less than 5 mm. in diameter, and one which is recorded as small. Three aneurysms were in the range of 5 to 9 mm.; four from 1 to 2 cm., and one over 2 cm. The size of two aneurysms was not recorded.

Seven aneurysms were found to be ruptured at postmortem examination. In one instance (Case 10) the aneurysm was unruptured and measured 1½ in. in diameter; this was a large sacculated aneurysm simulating a brain tumor. In another case there was no evidence of rupture of the aneurysm on inspection, but subarachnoid hemorrhage was present. Subarachnoid hemorrhage was noted in seven cases. Cerebral hemorrhage was also noted in seven instances. Hemorrhage had occurred into the frontal lobe in three instances, into the frontotemporal region in two, into the temporal region in one, and into the parietal region in one. Intraventricular hemorrhage was present in one case. In two instances, it was felt that the aneurysm had caused softening of the adjacent cerebral tissue by pressure. In one case, the softening occurred in the frontal lobe; in the other, in the hippocampal gyrus.

Evidence of arteriosclerosis of the circle of Willis was found in six instances. In one case, histologic studies revealed the aneurysm to be congenital in type. In one instance the aneurysm was mycotic in type and associated with metastatic encephalitis. Of the cases reported in the literature, 36 aneurysms of the middle cerebral artery were located on the right side and 32 on the left side; in 1 instance an aneurysm of the middle cerebral artery was bilateral, and in 5 instances the side on which the aneurysm occurred was not recorded. In seven instances the aneurysm was found at the junction of the middle cerebral artery with the internal carotid and/or anterior cerebral arteries; in four instances the aneurysm was located 1 cm. from the origin of the middle cerebral artery; in two it was located 2 cm. from the origin, and in one it was 3 cm. from the origin. The aneurysm was located at the base of the brain in 5 instances and in the Sylvian fissure in 26 cases; the aneurysm involved a small branch of the middle cerebral artery in 6 instances.

The aneurysm was reported as being small in 4 instances; less than 5 mm. in 7 instances; 5 to 9 mm. in 10 cases, 1 to 2 cm. in 13 cases, and more than 2 cm. in 5 cases. The unruptured aneurysms were in all instances larger than 5 mm. in diameter and in general showed a tendency to be larger than the ruptured aneurysms. Thirty-eight of the aneurysms were ruptured, and 10 were unruptured when they were examined.

Subarachnoid hemorrhage was reported in 24 cases, cerebral hemorrhage in 28 cases, and ventricular hemorrhage in 10 cases. The aneurysms tended to rupture into the temporal or frontal portion of the brain. Hemorrhage into the frontal lobe was recorded in 6 cases, frontotemporal in 1, temporal in 10, parietal in 2, temporoparietal in 1, and frontotemporoparietal in 1 case. The aneurysm ruptured into the basal ganglia in one instance, into the internal capsule and basal ganglia in one case, and into the region of the isle of Reil in two cases. Rupture occurred into an unrecorded portion of the hemisphere in two cases.

Summary of Clinical Findings

The age incidence of reported patients with middle cerebral artery aneurysm fell between 20 and 50 years, though there was a wide variability in age. In contrast to the cases reported in the literature, in our personal cases the average age was 49 years on admission to the hospital. Men predominated. In the majority of cases the symptoms were less than 1 week in duration, but symptoms were recorded of between 1 month and 15 years in duration prior to the

presenting symptoms of the aneurysm. Of the symptoms which appeared just prior to the acute onset, headache was most frequent, but it was of no localizing significance. Much less frequent were seizures, periods of unconsciousness, and transient weakness of the limbs.

The symptoms at the onset of the illness were not in themselves specific, but they seemed to indicate disturbance of cerebral function. Loss of consciousness was the most prominent symptom, usually with seizures. Hemiplegia was common but not constant, and headache was frequent at the onset of the illness. Neurologic examination usually revealed weakness or paralysis of the limbs, chiefly hemiplegia, associated with changes in the fundi frequently, and with other neurologic signs. The spinal fluid when examined was usually bloody or xanthochromic. In the majority of instances roentgenograms of the skull were of little value.

COMMENT

The clinical syndrome of aneurysm of the middle cerebral artery prior to rupture is ill-defined. This impression is clear from the 12 cases here reported, and it is amply supported by the experience of others in the literature. Beadles (1907), who analyzed 555 cases of aneurysm of the larger cerebral arteries, stated that he did not believe it possible to diagnose the presence of an aneurysm of the middle cerebral artery. In his analysis he found no evidence of aneurysm of this artery which had been diagnosed during life. His contentions were supported by Schmidt (1930), who stated that aneurysm of the middle cerebral artery seldom gave local symptoms and that such aneurysms were often impossible to diagnose before rupture. Krayenbuhl (1941) found no characteristic syndrome of the middle cerebral artery, and German (1947) reported that aneurysms of the middle cerebral, vertebral, and basilar arteries were problems for the future.

The detection of aneurysm involving the middle cerebral artery of either side is extremely difficult prior to rupture. In this respect the aneurysms of the middle cerebral artery differ greatly from those found elsewhere in the circle of Willis. In aneurysms arising in relation to most of the large vessels characteristic syndromes have been elucidated, so that the diagnosis may be determined on clinical grounds alone, often without benefit of arteriography. On the contrary, the symptoms referable to the aneurysms of the middle cerebral artery are indeterminate and nonspecific. This is the experience as illustrated not only by the cases here reported, but by the many already recorded in the literature. In the series here reported the only symptom of significance prior to rupture consisted of headache of a nonspecific character. This was true also of the cases recorded in the literature, which were characterized frequently by a history of headache, with seizures in a few instances and transient weakness in others. The symptoms were usually less than 1 week in duration, but varied from 1 week to 20 years. It is significant that there was nothing in the constellation of symptoms prior to rupture which could be utilized to point to the possibility of aneurysm. It is possible that the combination of headache, focal seizures, aphasia, and transient weakness might give rise to the consideration of middle cerebral artery aneurysm as a diagnostic possibility, but the symptoms can hardly be regarded as specific.

In the great majority of recorded instances of aneurysm of the middle cerebral artery, the diagnosis has been made after rupture. The onset under these circumstances has usually been with loss of consciousness, often with focal or generalized seizures, and hemiplegia. Neurologic examination has usually, but not always, revealed hemiparesis or hemiplegia, at times changes in the fundi, occasionally hemianopsia, and a scattering of other findings. Signs of meningeal irritation were frequent, due to subarachnoid hemorrhage. The spinal fluid has usually contained red blood cells or has been xanthochromic, and the pressure has tended to be elevated. Little information has been obtained from

radiological studies, except occasionally to encounter calcification.

Studies of the cases here recorded, as well as a survey of those analyzed in the literature, indicate that the diagnosis of aneurysm of the middle cerebral artery can be established after rupture but is difficult from clinical facts prior to rupture. The picture at such times in typical instances is that of sudden onset of loss of consciousness, often with headache and seizures, associated with evidences of meningeal irritation, hemiparesis or hemiplegia, or bloody or xanthochromic spinal fluid, in a middle-aged subject whose symptoms prior to onset have usually consisted of headache of less than a week's duration, but who may have had headaches extending over a period of 20 years. It is not possible to indicate a group of symptoms which could be regarded as significant for diagnosis prior to rupture. It is only possible to state that in patients with long-standing, unexplained headache, with occasional seizures, and transitory episodes of hemiplegia or aphasia the possibility of aneurysm of the middle cerebral artery should always be considered and arteriography performed. After rupture it is not always possible to be altogether certain whether the symptoms result from aneurysm, hemorrhage into a tumor, or cerebral hemorrhage of hypertensive origin. The difficulties arise in regard to the two last possibilities because of the presence of choked disc in some instances, and the differentiation can be made only on the basis of further studies.

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Ascending Fibers in Brain Stem Reticular Formation of Cat

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Moruzzi and Magoun [40] in 1949 demonstrated that stimulation of the brain stem of cats desynchronizes and activates the EEG in a manner paralleling arousal from sleep or alerting to attention. This effect was obtained from the medial bulbar reticular formation, pontine and midbrain tegmentum, dorsal hypothalamus, and subthalamus. From their electrophysiologic observations the authors assumed the structural substrate of the "brain stem activating system" to be a series of ascending reticular relays, which are activated by collaterals from sensory paths.

The observations of Moruzzi and Magoun [40] have subsequently been confirmed and extended by Magoun and his co-workers. The reticular activating system has been identified in the brain stem of the monkey,[17] and continued experimental research * has lent support to the assumption that the reticular activating system of the brain stem is "made up of a series of ascending relays coursing forward from the reticular formation of the lower brain stem through the mesencephalic tegmentum, subthalamus and hypothalamus and ventromedial thalamus." [32] These multisynaptic pathways appear to be independent of the large afferent projection systems. Electrophysiologic observations on conduction times within the system, shape of the potentials, and effects of successive stimuli,[19] as well as the effects of anesthetics,[20] indicate that the reticular activating system possesses a highly complex interneuron organization.

The ascending activating system has been shown to respond to stimulation of peripheral nerves and auditory stimuli,† to splanchnic nerve stimulation,[17] and to visual,[17] olfactory, and vagal stimuli.[16] There appears to be no organization in the area of the activating system with regard to the segregation of incoming fibers into discrete sensory modalities, since all systems feed into it diffusely throughout its extent.‡ The sensory impulses reaching the activating system are assumed to enter it via collaterals § from the specific sensory paths. Such "collateral" spread of impulses to the reticular formation has been noted previously by several workers, thus from parts of the auditory system,‖ from trigeminal pathways,¶ and following stimulation of peripheral nerves.# That impulses from different sources may even converge on the same reticular units appears from the recent works of von Baumgarten and Mollica,[4] Scheibel and co-workers,[51] and Amassian and DeVito.[3]

While extensive electrophysiologic studies have largely clarified the functional properties of the reticular activating system, little interest appears so far to have been devoted

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* References 18, 19, 30, 31, and 53.

† References 17, 19, and 53.

‡ References 17, 19, and 53.

§ References 17 and 53.

‖ References 1, 28, and 46.

¶ References 33 and 35.

References 5 and 33.

to its structural organization. The studies of Ramón y Cajal [15] and others make it appear likely that synaptic connections within the reticular formation of the brain stem may be extremely complex, and some anatomic evidence for collateralization to the reticular formation from large ascending fiber systems is also available, as will be considered in the discussion of the present paper. Even if the term "collateral" by the physiologists is being "employed in a general, rather than a strict anatomical sense," [53] so far the available anatomic information appears to be compatible with the concept of the structural organization of the ascending reticular activating system deducted from physiologic observations.

However, there are indications in the anatomic literature that the reticular activating system may be organized in a more complex manner than is assumed in current physiologic writings. Thus, Probst [45] in Marchi studies in the dog described fibers from the spinal cord ascending in the brain stem ventral to the medial longitudinal fasciculus and terminating by means of collaterals on the large cells of the pontine reticular formation at the level of the motor trigeminal nucleus. More recently, Morin, Schwartz, and O'Leary,[38] in the monkey, described spinoreticular fibers to the lateral part of the medullary reticular formation and to the area between the root fibers of the sixth and seventh cranial nerves, and their findings were confirmed in the cat by Johnson.[26] It is conceivable that such fibers, in addition to collaterals from specific ascending systems, may be responsible for the activation of the reticular formation following stimulation of spinal nerves. Furthermore, there is reason to assume that there may be within the brain stem reticular formation long ascending fibers which take origin from cells of the reticular formation proper. Thus, Russell and Johnson [50] and Morin [37] recently confirmed Lewandowsky's * demonstration of a reticulothalamic tract. Since these authors, however, made lesions of the reticular formation, it is possible that some or all of the degenerating ascending fibers observed may be derived from the spinal cord.

The present study was undertaken in an attempt to decide whether ascending reticular fibers really exist. The only approach to this problem which can be expected to give reliable results is to investigate whether acute retrograde changes occur in cells of the reticular formation following lesions of higher levels of the brain stem. The modified Gudden method, worked out previously,[8] was employed, since it has proved satisfactory in previous studies of afferent cerebellar connections. By using this method, it has been possible to establish the existence of ascending reticular fibers, and also to obtain information of their sites of origin, their length, and the types of neurons projecting rostrally.

MATERIAL AND METHODS

The experimental animals used in this investigation have been operated upon by Dr. A. Torvik for the study of connections of certain brain stem nuclei. By insertion of a blunt spatula through a supratentorial craniotomy, lesions were made at different levels of the upper brain stem in kittens aged 8-9 days. The operations were made with the animal under pentobarbital (Nembutal) anesthesia and under sterile precautions. Penicillin was given postoperatively, and no cases were complicated by infection. In order to have the animals survive for a sufficiently long time, it is essential to secure an adequate supply of fluid either by tube feeding or by subcutaneous injection of Ringer's solution. If this is done and the kittens are kept warm, they will usually be in good condition throughout the postoperative period.

The animals were killed by exsanguination under chloroform anesthesia 4-13 days after the operation, according to the modified Gudden method.[8] A survival time of 7-8 days turned out to be optimal, since at this stage the retrograde cellular changes are most characteristic in the cells of the reticular formation of the brain stem. Of altogether 20 animals operated upon, 14 presented sufficiently clear-cut alterations to be utilized in this study.

After the animal was killed, the brain with the brain stem and cerebellum was immediately dissected free, fixed in 96% alcohol, and subsequently embedded in paraffin. The entire brain stem from well above the level of the lesion, with the cerebellum attached, was cut in serial sections of 15μ. Every fifth section was mounted and stained with

* Lewandowsky,[29] cited by Morin.[37]

thionine. Some of the remaining sections were used for supplementary Nissl sections to check particular areas more closely. The altered cells observed under the microscope were entered in drawings of sections, taken at regular intervals by means of a projection apparatus. Only cells showing the fully developed picture of retrograde changes, as seen below, have been taken into consideration.

As controls were used the brains of some normal kittens and of several kittens of the same age subjected to ablations of parts of the cerebellum but otherwise treated in the same way as those employed in the present investigation.

RESULTS

Reticular Formation of the Brain Stem

In spite of the efforts of many workers, we have as yet not arrived at an entirely satisfactory topographical subdivision of the reticular formation of the brain stem. It is true that several groups of cells may be more or less clearly defined by purely cytoarchitectonic criteria, as has been shown most recently by Olszewski and collaborators.† However, the grouping of cells on this basis in a so diffusely structured part of the brain as the reticular formation will of necessity be to some extent arbitrary. As long as it is not known whether individual cell groups outlined in this way are distinguished also by having particular afferent and efferent connections, differences in synaptic patterns, etc., one should be cautious in attributing too much importance to smaller, diffusely outlined cell groups or diffuse borders between groups. As far as our personal experience goes, the cell groups of the reticular formation which possess fiber connections with particular other regions are those which can clearly be identified in Nissl sections as well-circumscribed nuclei, namely, the lateral reticular nucleus, or nucleus funiculi lateralis, the nucleus reticularis tegmenti pontis of Bechterew, and the recently described paramedian reticular nucleus of the medulla oblongata.[10] These nuclei send all their efferent fibers to the cerebellum.‡

In the present study we are concerned with the remainder of the reticular formation, making up, so to speak, the central core of the brain stem. As will be seen below, large areas of this, containing cells of different types and comprising several loosely defined aggregations of cells, appear to be similar with regard to their fiber connections. The distribution of the alterations observed will, therefore, be described with reference only to projection drawings of particular sections which are sufficiently detailed to permit identification of the areas containing changed cells. Possible correlations with nuclear groups described by Olszewski and collaborators will be considered in the discussion.

The cells of the reticular formation proper of the brain stem may, somewhat arbitrarily, be classified according to size, as they appear in Nissl sections, as giant, large, medium-sized, and small cells. The cells also differ with regard to their shape, their pattern of Nissl substance, and other features. As an example, Figure 1 shows the four types of cells present in the pontine reticular formation. In other parts there are other types of cells. Concerning their occurrence, it is to be noted that no area is characterized by having cells of one type only. But the relative number of cells of the four types shows considerable regional variations. Thus, the most conspicuous elements, the giant cells, are absent in the mesencephalic reticular formation, but are present throughout the pons and the upper third of the medulla. They are found almost exclusively in the medial two-thirds of the reticular formation.

Elements called here large cells (Fig. 1) are relatively abundant in the reticular formation of the pons and medulla, particularly in the ventral regions of the latter, but they are almost absent in the mesencephalic reticular formation, which is made up chiefly of medium-sized and small cells.

Certain cell groups, described by some as parts of the reticular formation, by others as particular nuclei, present more or less characteristic cytoarchitectonic features in Nissl sections. Since convincing changes have not been observed in most of these, such as the dorsal and ventral tegmental nuclei of

† References 36, 42, and 43.

‡ References 9, 10, 12, and 13.

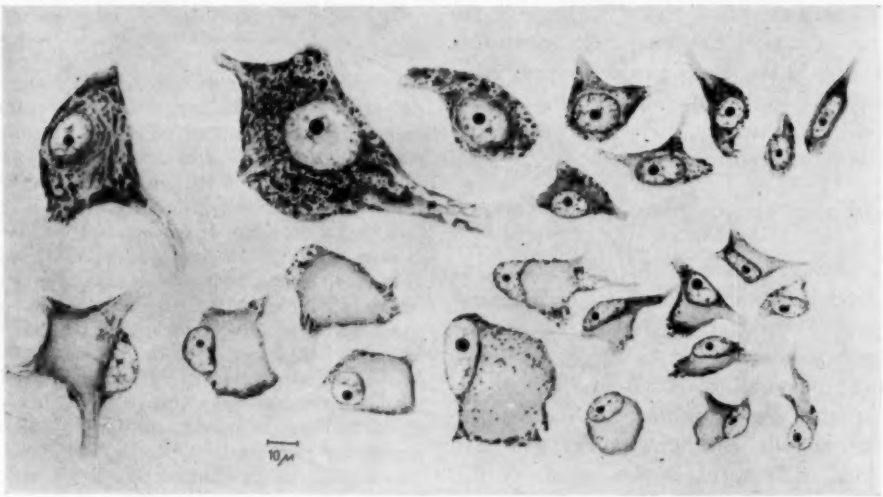

Fig. 1.—Camera lucida drawings of cells from the pontine reticular formation in the area surrounding the root fibers of the abducent nerve in 14-day-old kittens. Above, specimens of normal cells, arbitrarily classified here as giant, large, medium-sized, and small cells. The largest giant cell drawn is an unusually large specimen. Below, cells of the same types showing the fully developed picture of retrograde changes. Changed huge giant cells have not been seen.

Gudden and the central superior nucleus of Bechterew, they will not be considered here. The raphe nucleus, which in many places fuses with the reticular formation proper, probably should be considered a particular part of this. In favor of this interpretation is the occurrence of retrograde changes in it in the cases to be described below. Figure 3*e* shows some normal cells of the raphe nucleus of the medulla oblongata.

Retrograde Cellular Changes in the Reticular Formation

Following lesions of the upper brain stem a considerable number of cells in its more caudal parts present characteristic changes. These are most conspicuous in the very large cells (Figs. 1 and 3*a*, *b*, *c*, and *f*), which are here referred to as giant cells. Their cytoplasm shows a marked tigrolysis and acquires a homogeneous, milky appearance, while the nucleus is displaced to the periphery of the cell and may be considerably flattened. The nuclear membrane is thinned and becomes indistinct, and the nucleolus may be reduced in size. Similar changes are also found in large, medium-sized, and small cells in the reticular formation (Figs. 1, 3, and 5). The changes are less dramatic in the small and medium-sized cells, and on account of their scanty Nissl substance, the tigrolysis is less conspicuous. Since, furthermore, in young animals the nucleus is often normally situated peripherally in these cells, great care has been taken in evaluating this type of cells, and attention has here also been given to signs of disintegration of cells, betraying itself by a complete lack of Nissl substance and disappearance of cell contours. Where a larger number of cells is affected there are usually also signs of activation of glia cells.

In all cases cells are also present which show intermediate changes between the normal appearance and the fully developed alterations. To avoid any possible error of interpretation, such cells have not been taken into account in the recording of cell changes.

On account of the characteristic appearance of the altered cells (Fig. 1), it is considered safe to interpret the cellular alterations as true retrograde changes, developing as a consequence of transection of axons. The occurrence of typically altered cells following lesions of the upper brain stem is, therefore, taken to indicate that there are cells in the reticular formation of the brain stem which

have axons ascending above the lesion in the particular case. Retrograde cellular changes occurring in the specific rostrally projecting nuclei, such as the superior olive, the nucleus of Goll and Burdach, and other nuclei, will not be considered in the present study.

Sites and Types of Rostrally Projecting Neurons

Following lesions of the brain stem at the level between the inferior colliculus and the pons, characteristic retrograde cellular changes were observed in all four animals in this group. Cells of all types were changed. Apart from slight variations in the number of altered cells, depending at least in part on small differences in the extent of the lesions, the findings were identical in all cases. The following case will be described as a representative example.

Cat D 4.—Operated upon when 8 days old; killed seven days later (Figs. 2 and 3).

A blunt spatula was inserted immediately above the tentorium and was moved ventrocaudally in order to make a right hemisection of the brain stem. Serial sections show that ventrally the lesion extends also considerably across the midline, and caudally it encroaches upon the rostral part of the pons (Fig. 2).

In serial sections through the brain stem, typical retrograde cellular changes are found in the reticular formation from the level of the lesion to the caudal end of the medulla. The changes are equally marked on the two sides. A certain number of giant cells (coarse dots in the drawings of Fig. 2) are changed (Fig. 3*a-c*), but also large, medium-sized, and small cells present unequivocal changes (Fig. 3*d*, *f*, and *g*).

In spite of their occurrence throughout the entire length of the brain stem reticular formation, the altered cells are more abundant in certain regions. The lateral third of the reticular formation, medial to the principal and spinal nuclei of the trigeminal nerve, is almost free of such cells. On the whole these are seen in transverse sections within an approximately triangular area, having its top at the region of the hypoglossal and abducent nuclei and its lateral side somewhat lateral to the plane indicated by the root fibers of the nerves mentioned. In some places (Fig. 2) the area containing altered cells approaches the ventral surface of the medulla, but otherwise it is bordered ventrally by the specific nuclei and fiber tracts, such as the inferior and superior olives, the pontine nuclei, and the trapezoid body.

The quantitatively most important changes are found around the abducent nerve (Drawings *2-4* in Fig. 2 and Fig. 3*f*), where also the greatest number of altered cells are situated. Here the pathologic cells form a sort of wide cuff ensheathing the root fibers of the nerve. Another site of marked changes is the area dorsal and dorsolateral to the rostral third of the inferior olive (Drawing *6* in Fig. 2). In this area there are many large cells, and a considerable number of these, as well as many small and medium-sized cells, are altered (Fig. 3*d*). Connected with this area is a smaller collection of changed cells, chiefly medium-sized ones, surrounding the nucleus ambiguus (Drawing *6-8* in Fig. 2; Fig. 3*g*). In the caudalmost part of the medulla the number of changed cells is small. In the maximally changed areas it is estimated that approximately one-third of all cells present are pathologic.

In addition to the changed cells in the reticular formation, mention may be made of the occurrence of similarly altered cells in parts of the raphe nucleus. They are found chiefly a little above and at the level of the rostral half of the inferior olive (Drawings *6-7* in Fig. 2; Fig. 3*e*), but also ventrally in the pontine raphe. These ventral parts of the raphe nucleus are continuous with the changed areas of the reticular formation at these levels.

No retrograde cells were found in the lateral reticular nucleus, the paramedian reticular nucleus, or the nucleus reticularis pontis of Bechterew, which have all previously been shown to project onto the cerebellum.§

Findings similar to those described for Cat D 4 were made in three other kittens (Cats D 3, D 5, and D 7), having lesions differing only slightly from that in Cat D 4. They were all operated upon when 8 days old and killed after five, seven, and eight days, respectively.

The consistent findings in these four cases permit the conclusion that there are in the reticular formation of the medulla oblongata and lower pons a considerable number of neurons with ascending axons which pass to more rostral levels of the brain stem. These neurons are of all types—giant, large, medium-sized, and small cells. Although distributed in the medial two-thirds of the reticular formation in its entire extent throughout the lower pons and medulla, they are particularly abundant at certain levels: around the root fibers of the abducent nerve

§ References 9, 10, 12, and 13.

and in the region dorsal and dorsolateral to the rostral third of the olive. Connected with the latter area is a smaller collection of cells, surrounding the nucleus ambiguus and the ventral part of the raphe nucleus of the medulla.

It is of interest to compare the findings described above with those made in cases with lesions at more rostral levels, and with unilateral lesions.

CAT D 6.—Operated upon when 8 days old; killed eight days later (Figs. 4 and 5).

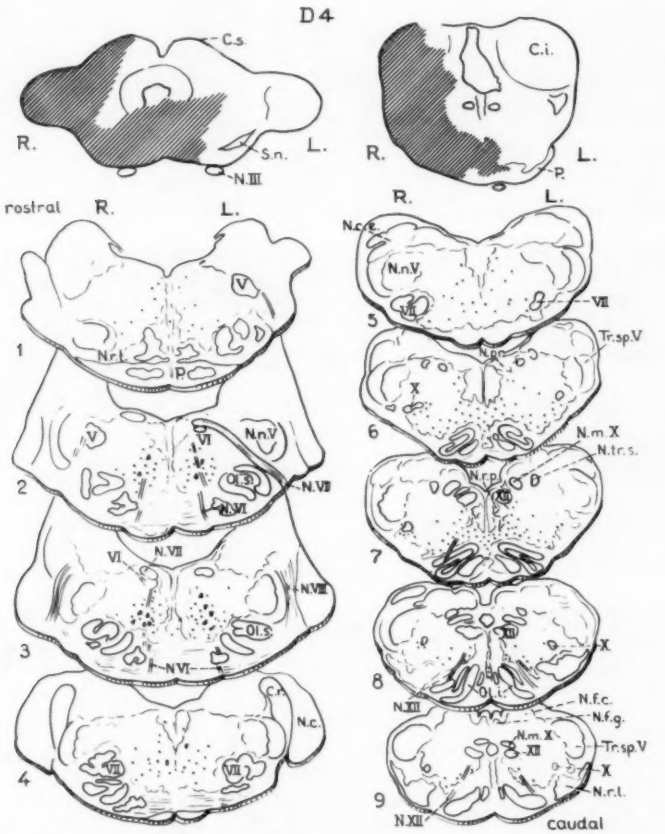

Fig. 2.—Diagram of the findings in Cat D 4. Above, two drawings of the lesion (hatchings). Below, drawings of a series of transverse sections through the lower brain stem, taken at equal intervals. In the drawings, made by means of a projection apparatus, cells showing retrograde changes have been entered—changed giant cells as heavy dots, changed cells of all other types as small dots. Each dot represents two to three cells, as seen in 15μ-thick sections.

The following abbreviations are employed in Figures 2, 4, 6, 7, and 8: *B*, nucleus of Bechterew; *B. c.*, brachium conjunctivum; *C. i.*, inferior colliculus; *Ca.*, internal capsule; *CM*, centromedian thalamic nucleus; *C. r.*, restiform body; *C. s.*, superior colliculus; *D*, nucleus of Deiters; *F. l. m.*, medial longitudinal fasciculus; *GL*, lateral geniculate body; *GM*, medial geniculate body; *H*, hypothalamus; *L*, left; *MD*, dorsomedial thalamic nucleus; *N. c.*, cochlear nucleus; *N. c. e.*, external cuneate nucleus; *N. f. c.*, nucleus of Burdach; *N. f. g.*, nucleus of Goll; *N. l. l.*, nucleus of lateral lemniscus; *N. m. X.*, dorsal motor vagus nucleus; *N. mes.*, mesencephalic V nucleus; *N. n. V.*, principal sensory trigeminal nucleus; *N. pr.*, nucleus praepositus hypoglossi; *N. r.*, red nucleus; *N. r. l.*, lateral reticular nucleus, or nucleus funiculi lateralis; *N. r. p.*, paramedian reticular nucleus; *N. r. t.*, nucleus reticularis tegmenti pontis of Bechterew; *N. t. d.*, dorsal tegmental nucleus; *N. t. v.*, ventral tegmental nucleus; *N. tr. s.*, nucleus of solitary tract; *N. tr. sp. V*, nucleus of spinal tract of trigeminal nerve; *N. III*, *N. VI*, *N. VII*, *N. VIII*, *N. XII*, root fibers of cranial nerves; *Ol. i.*, inferior olive; *Ol. s.*, superior olive; *P.*, pontine gray matter; *R.*, right; *Rt.*, reticular thalamic nucleus; *S. n.*, substantia nigra; *To.*, optic tract; *Tr.*, trapezoid body; *Tr., sp. V*, spinal tract of trigeminal nerve; *III, IV, V, VI, VII, X, XII*, motor nuclei of cranial nerves; *X*, nucleus ambiguus.

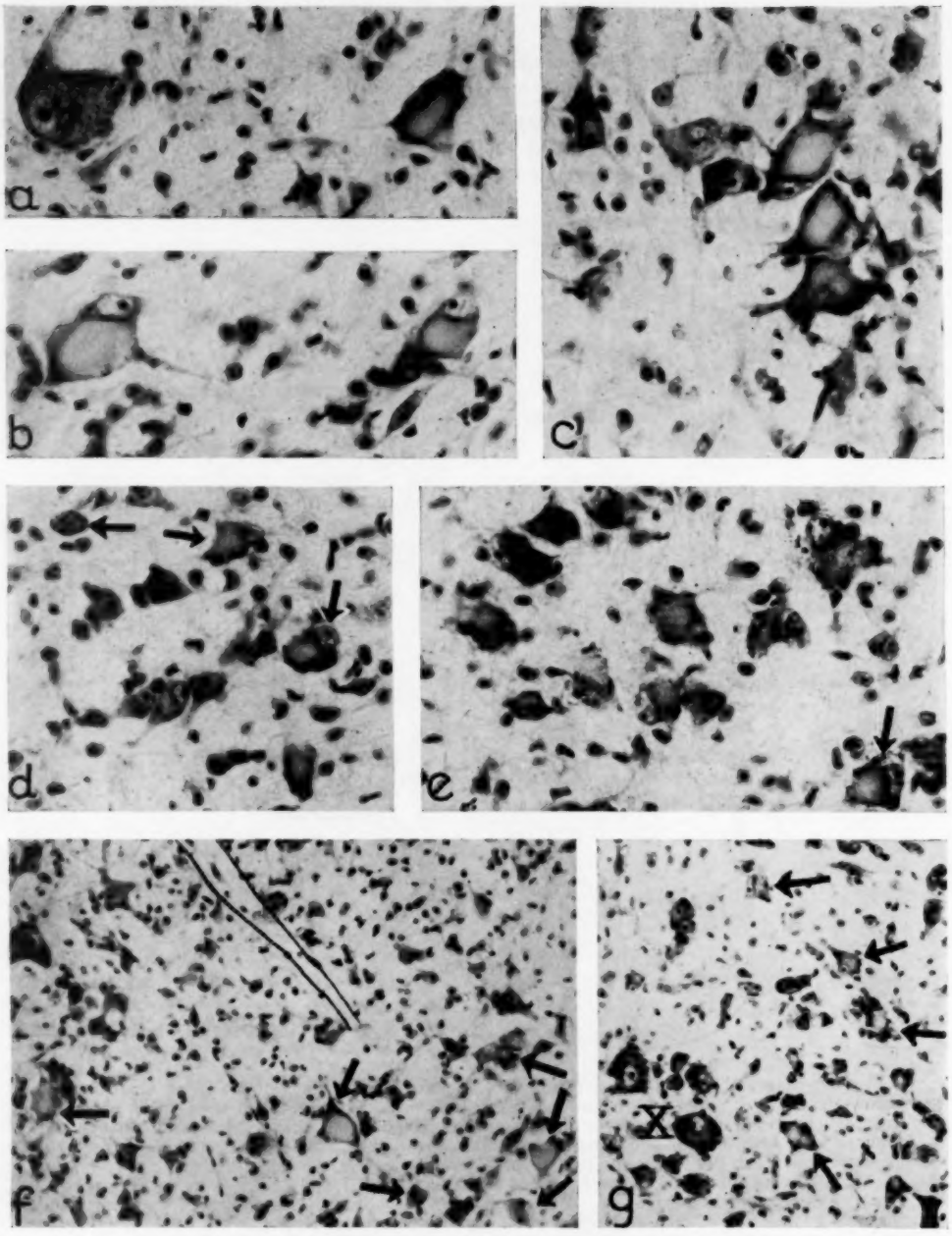

Fig. 3.—Photomicrographs of retrograde cellular changes in Cat D 4.

(*a*) A normal and a changed giant cell at the level of the abducent nerve. × 300.

(*b*) Two giant cells from the same area, showing fully developed retrograde changes. × 300.

(*c*) Changed cells from the reticular formation slightly dorsal to the superior olive at level of Drawing *3* of Figure 2. × 300.

(*d*) Large and medium-sized altered cells (arrows) from the medullary reticular formation, slightly lateral to the hypoglossal root fibers, corresponding to the level of Drawing *7* in Figure 2. Some glial reaction. × 300.

(*e*) A cell with typical retrograde changes (arrow) in the raphe nucleus of the medulla oblongata (level of Drawing *6* in Figure 2). Some normal cells and some with indefinite changes are also seen. × 300.

(*f*) Changed cells (arrows) of different types around the abducent nerve (shown in outline). × 140.

(*g*) Changed cells (arrows) in the vicinity of the nucleus ambiguus (*X*). × 140.

In this animal the lesion is practically limited to the right half of the brain stem, extending only a little across the midline in the dorsal hypothalamic region. Caudally, it reaches to the level of the lower part of the red nucleus, sparing, however, the medial half of the brain stem here.

In the serial Nissl-stained sections retrograde changes are found in cells of all four types in the reticular formation. Figure 5*a* shows large and medium-sized cells from the pons. The distribution of altered cells (Fig. 4) in the lower pons and medulla corresponds to that in the preceding cases, but their number is somewhat less, and the changes are more marked on the side of the lesion.

In sections through the transitional area between the upper pons and the lower mesencephalon (Drawings *1-2* in Fig. 4), the number of cells showing retrograde changes (Fig. 5*b* and *c*) is rather modest. Here, also, however, they occur chiefly in the medial two-thirds of the reticular formation, as well as in the raphe.

A similar lesion was present in Cat D 20, operated upon when 8 days old. This animal was killed after four days, and the number of altered cells for this reason is less than in Cat D 6 (Fig. 4). However, the distribution of changed cells is essentially similar.

The findings in these series show that at least the majority of the ascending reticular fibers from the medulla and pons pass farther rostral than to the lower mesencephalon. Furthermore, it is learned that there are also in the reticular formation at the transition between the pons and the mesencephalon neurons sending their axons in a rostral direction. Their number is, however, rather modest, and the majority of these cells, in contrast to those in the pons and medulla, are of the medium-sized type, in agreement

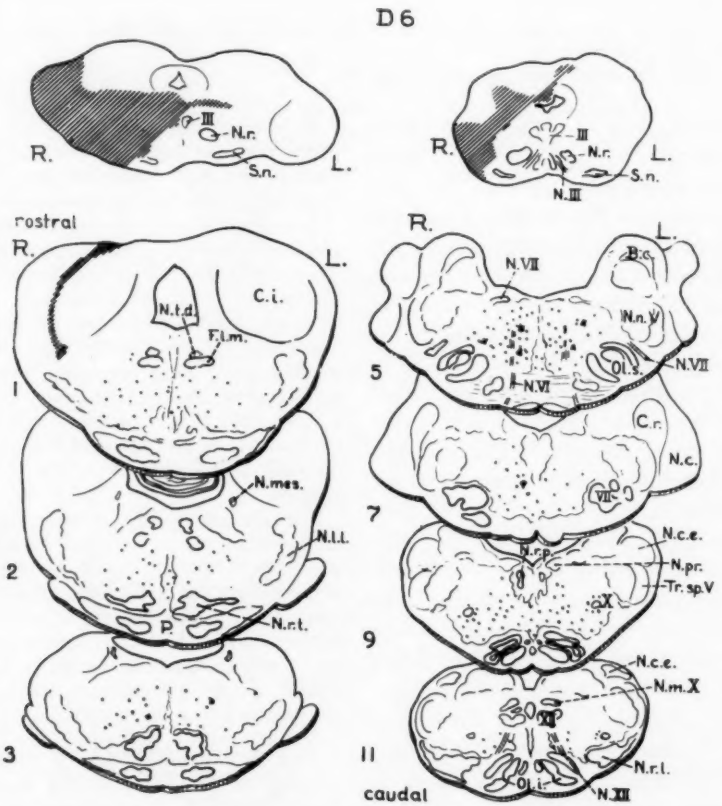

Fig. 4.—Diagram of the findings in Cat D 6 after the same principles as those in Figure 2. The interval between the caudal sections drawn is twice that between the rostral ones, as appears from the numbering of the drawings. For abbreviations see list in legend for Figure 2.

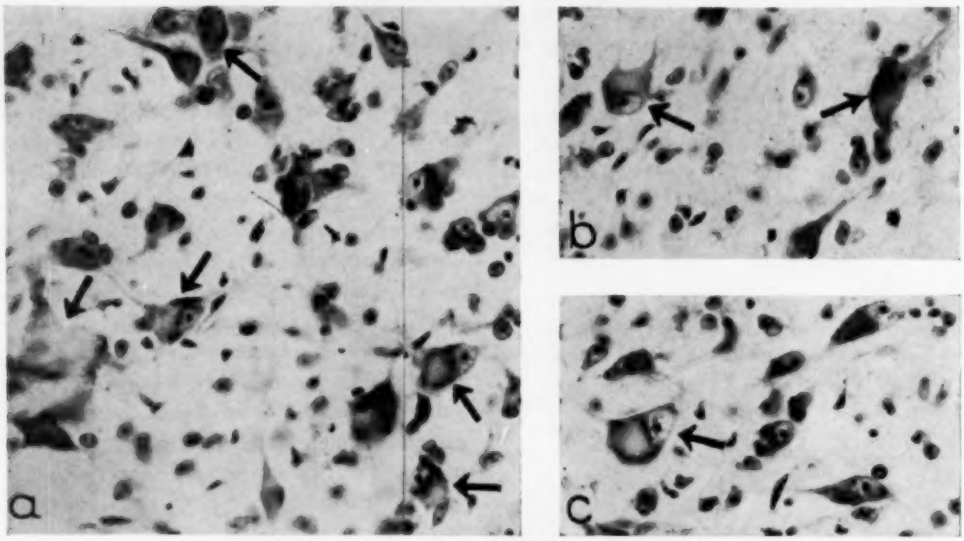

Fig. 5.—Photomicrographs of retrograde cellular changes in the reticular formation of Cat D 6. × 300.

(*a*) From the level of the abducent nerve. A changed giant cell (out of focus) and large and medium-sized cells.

(*b* and *c*) From the lower mesencephalon.

with the normal lack of giant cells and the small number of large cells at this level of the reticular formation.

The asymmetrical distribution of changed cells indicates that more fibers ascend uncrossed than crossed, since the small involvement of the left half of the brain stem in Cat D 6 can scarcely be responsible for the rather abundant changes on the left. That there is some preponderance of uncrossed ascending fibers is substantiated also by the findings in other cases (cf. below). The somewhat less intense degeneration in the pons and medulla in Cat D 6 (Fig. 4) than in Cat D 4 (Fig. 2) most likely is to be explained by the lesion being almost unilateral in the former case, but it may also indicate that some of the ascending fibers from the medulla and pons terminate in the upper pons. However, the quantitative differences may also simply be an expression of individual differences among the experimental animals with regard to the speed of development of the retrograde changes.

CAT D 22.—Operated on when 8 days old, killed six days later (Fig. 6).

In this case the lesion (Fig. 6) involves the entire posterior half of the right thalamus and extends into the rostralmost part of the mesencephalon. Its most caudal point is found ventrally at the upper pole of the red nucleus. Rostral to the levels shown in Figure 6, the lesion extends more across the midline and involves the medioventral part of the left thalamus.

In the serial sections through the brain stem, retrograde cellular changes are found in the medulla and pons in the same areas as in the cases described above (Drawings *7*, *12*, and *18* in Fig. 6). The number of altered cells is practically the same as in Cat D 6, and is a little larger on the right than on the left. Cells of all types are affected.

The changes in the mesencephalon are less marked than in the pons and medulla, but there are on both sides a certain number of changed medium-sized and small cells. The difference between the two sides is less at this level than in the pons and medulla. The distribution of the altered cells is seen from Figure 6. A considerable number of cells are changed in the area between the emerging root fibers of the oculomotor nerve.

A lesion resembling that in this case is present in Cat D 16, killed after 12 days. The findings concerning the occurrence of retrograde cellular changes are in agreement with those reported above. It is seen from

these series that many, if not all, of the ascending reticular fibers taking origin in the medulla and pons are long, since they pass rostrally beyond the mesencephalon. Furthermore, other ascending fibers come from the mesencephalic reticular formation, but the contribution of this part of the brain stem to the ascending reticular fibers appears to be quantitatively less impressive.

The method employed in the present study does not give information of where within the brain stem the ascending fibers pass, nor does it permit decisive conclusions concerning the terminal area of these fibers. However, some suggestions concerning these items may be made from a comparison of cases having lesions in different regions. Some relevant examples are shown in Figure 7. Since in all cases the retrograde cellular changes in the brain stem are found in identical areas of the reticular formation, these are represented only by a sample drawing from the maximally changed level, in order to show the relative intensity of changes in the different cases, as well as differences between the two sides in each case.

From Figure 7 it will be seen that a lesion destroying most of one thalamus (Cat D 23, operation at 8 days; killed after eight days) is followed by very slight changes. In Cat D 9 (8 days—9 days), having also an extensive thalamic lesion, which, however, spares the ventral and medial regions, as

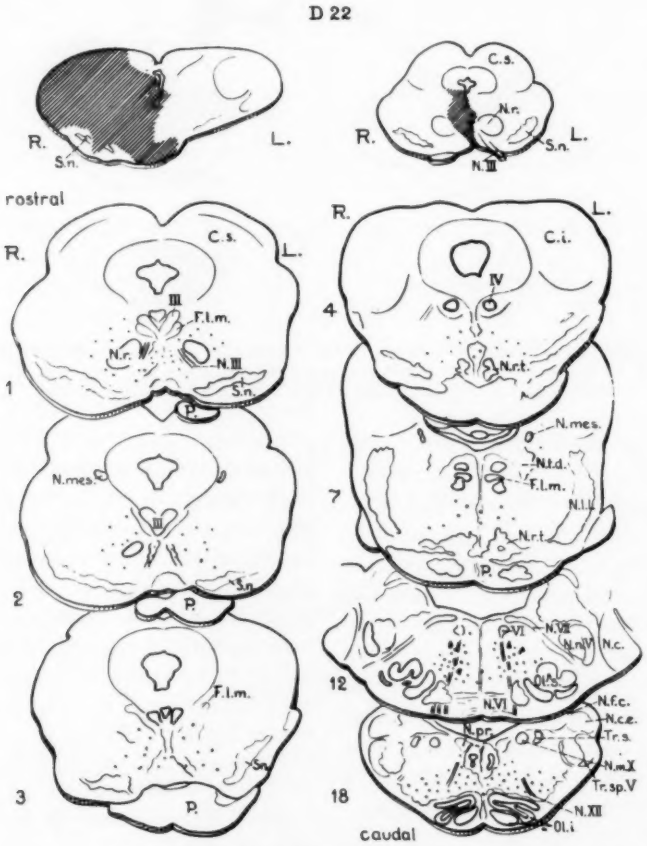

Fig. 6.—Diagram of the findings in Cat D 22 after the same principles as those in Figure 2. The relative interval between the sections drawn will be seen from the numbers of each drawing. For abbreviations see list in legend for Figure 2.

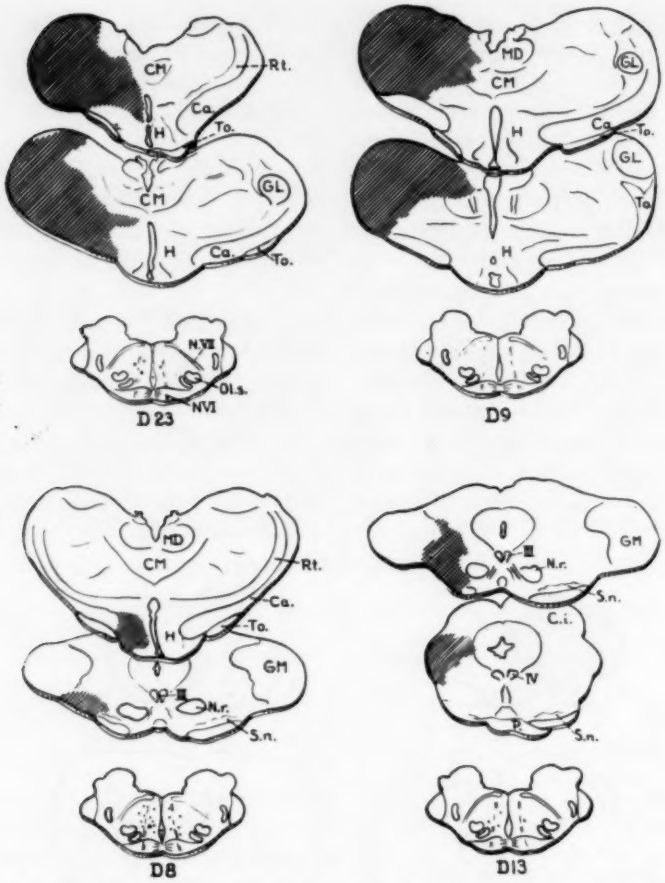

Fig. 7.—Diagram showing the lesions and the distribution of the ensuing retrograde changes in four cases with different lesions. The changes in each case are represented in a sample drawing from the level of the abducent nerve. For abbreviations see list in legend for Figure 2.

well as the hypothalamus, no changes are found in the brain stem reticular formation. On the other hand, when the posterior hypothalamus is damaged (Cat D 8, 8 days—12 days), the changes in the reticular formation are considerable. (In Cat D 8 there was also a small lesion on the lateral surface of the mesencephalon, but a comparison with other series, e. g., Cat D 13 [Fig. 7], shows that this lesion can scarcely be responsible for the marked changes.) It should be noted that the thalamic lesion in Cat D 23 (Fig. 7) encroaches also a little on the hypothalamus.

These findings lend support to the assumption that at least the majority of the long ascending fibers from the reticular formation of the brain stem reach the posterior hypothalamus. Whether they terminate here or pass through it only cannot be decided, but the very slight changes following large lesions of the thalamus point to the former possibility as the more likely. However, the possibility of some fibers passing through or ending in the medial thalamic nuclei, e. g., the centromedian nucleus, cannot be excluded (cf. Cat D 23, Fig. 7). The absence of changes in the reticular formation following large lesions of the cerebral cortex (Cat D 25, 8 days—8 days, and Cat D 26, 8 days—6 days) makes it little likely that the fibers pass as far as this.

According to the findings of Lewandowsky,[29] Russell and Johnson,[30] and Morin,[37]

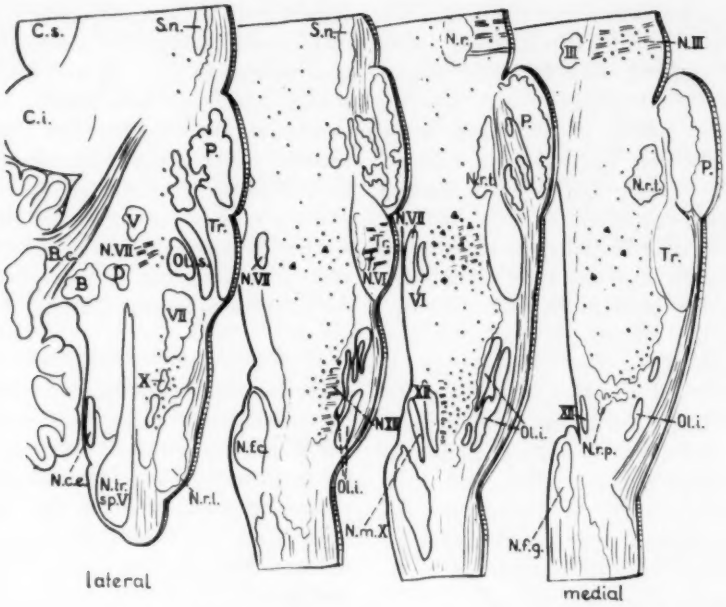

Fig. 8.—Diagram summarizing the findings made in this study. The distribution of cells with ascending axons in the brain stem reticular formation is shown as projected on a series of sagittal sections. Large dots represent giant cells; small dots represent cells of other types. Note: Giant cells are present also at other levels, but are not changed following rostral brain stem lesions.

the ascending fibers of the reticular formation appear to terminate in the centromedian nucleus of the thalamus, the subthalamus, and, according to Russell and Johnson, the arcuate nucleus as well. The findings made in the present study, although not decisive, are compatible with the observations of these authors. Likewise, our findings agree with the statement of these authors, that in the midbrain the ascending reticular fibers pass in the area usually allotted to the so-called central tegmental tract. This appears from the findings in Cat D 13 (8 days—12 days, Fig. 7), in which only very slight changes were found in the reticular formation. The lesion in this case encroaches only slightly on the area mentioned.

The differences between the degeneration in the two halves of the brain stem in the cases shown in Figure 7 are in agreement with the conclusion made above that the proportion of homolaterally ascending reticular fibers is greater than the crossing contingent.

Figure 8, summarizing in a semidiagrammatic way the results of the present study, shows the concentration of ascending reticular neurons at certain levels of the brain stem and their scarcity in its lateral areas.

COMMENT

Retrograde Cellular Changes in the Reticular Formation

The cellular alterations occurring in the reticular formation at levels caudal to lesions of the brain stem are typical examples of so-called retrograde cellular changes. Changes of the same type are seen in other cell groups of the reticular formation following lesions of the cerebellum,‖ as well as following lesions of the spinal cord (unpublished observations). This finding substantiates the belief that the cellular changes described here are due to transection of ascending axons.

As mentioned above, only cells presenting the fully developed retrograde changes have been taken into account. This implies that

‖ References 9, 10, 12, and 13.

usually only a certain number of cells having actually suffered transection of their axons have been registered, since it is well known that the retrograde changes may develop with different speeds in individual nerve cells of a nucleus. Furthermore, cells of different types show the maximal changes at varying intervals after the lesion. While, therefore, the cells recorded as changed in our cases always represent only a minimum of those possibly present, the procedure employed has the advantage that subjective factors involved in the classification of slighter alterations are eliminated. Since the retrograde changes in the smallest cells are difficult to evaluate, it is quite possible that our estimates of changed cells of this type are too conservative. It also follows from the individual variations that quantitative comparisons of findings in different cases can be made only with great reservations.

In spite of the limitations inherent in the method employed here, it is nevertheless the best available at present for the study of the problem under consideration. The search for late changes, consisting in loss of cells, cannot be expected to give results in a study like this, since the diffuse scattering of neurons with ascending axons among cells of other types would make it impossible to identify a numerical decrease of cells, the more so since the bilaterality of the changes after unilateral lesions excludes a comparison of one side with the other. The features mentioned probably explain why Niemer,[41] studying the chronic changes in the brain stem after transection at various levels, recognized only ascending fibers from the "nucleus reticularis lateralis medullae" and from large reticular cells in the caudal medulla. Clear results can be expected only from a study of the acute stages of the retrograde changes. But even these may be little clear-cut in adult animals.

That very young kittens have been used in the present study is because acute retrograde changes develop more easily and are clearer-cut in these than in adult animals.¶ However, in such young animals the nucleus may normally often have a somewhat peripheral location in the cell, and the Nissl substance is less abundant than in adults. This emphasizes the need for recording only cells showing the fully developed changes as positive. Finally, it should be mentioned that absence of changes in a particular case is not decisive, since individual differences with regard to the speed of the development of the changes are considerable.

Reticular Neurons Projecting Rostrally

Having employed the strict criteria outlined above, we feel justified in stating that our findings demonstrate the presence within the brain stem reticular formation of neurons projecting rostrally. They thus support the observations made by Lewandowsky,[29] Russell and Johnson,[50] and Morin,[37] who, following lesions of the brain stem, observed ascending degenerating fibers in Marchi sections. While this approach gives no information of the origin of the fibers, the method used here, on the other hand, allows one to determine with great accuracy the origin of the fibers, but concerning their course and termination only suggestions can be made. Our findings concerning the partial crossing of the ascending reticular fibers are in agreement with the observations by the authors mentioned, and also agree with those of Cajal.[15]

The most remarkable finding in the present study is the demonstration that there are within the medullary, pontine, and mesencephalic reticular formation of the brain stem neurons having long ascending axons. On the basis of our material we cannot say whether some ascending axons terminate in the brain stem itself, but it is clear that a considerable proportion of them, even from the medulla, pass beyond the mesencephalon. The findings of Niemer[41] make it appear possible, however, that at least in the lower medulla some of the ascending neurons may have short axons. Although we have found relatively few changed cells in the mesencephalon, the number of rostrally projecting neurons at this level may well be larger than

¶ References 7 and 8.

appears from our study on account of the difficulties in recognizing changes in cells of the smallest type.

It is of considerable interest that retrograde changes occur in cells of all types. However, no specimen of the largest type of giant cells (Fig. 1) was found to be changed (in contrast to cases with spinal cord lesions). Provided the general assumption is correct that large cells have thick axons and small cells thin axons, it must be concluded that the ascending reticular fibers have diameters varying within a wide range and consequent variations in conduction velocities. It may be recalled, in this connection, that the reticular nuclei projecting onto the cerebellum # show the same feature, cells of all types sending their axons to the same goal.

The number of rostrally projecting neurons in the reticular formation is considerable. Our estimate is that in the areas particularly rich in ascending neurons (Fig. 8), approximately one-third of all giant, large and medium-sized cells are changed after appropriate rostral lesions. Since our recordings give minimal values (cf. above), it is conceivable that the actual number of neurons with ascending axons may, in fact, be appreciably larger. The less characteristic changes in the smallest cells make quantitative estimates of them unreliable. The common occurrence of cells with ascending axons in the brain stem reticular formation is evident also from the Golgi studies of Held [24] and Cajal.[15] They have been described also in other vertebrates,[27] even in the myxine.[25]

According to Cajal, many reticular cells have axons dichotomizing in an ascending and a descending branch. It is an interesting problem whether such cells would be subject to retrograde changes following transection of only one of their axonal branches. It is generally assumed that preservation of collaterals proximal to the place of transection of an axon will protect its perikaryon from reacting with retrograde changes. A preservation of one of the two dichotomizing branches of an axon might be expected to give even better protection. Should this be the case, one might assume that all reticular cells showing retrograde changes following lesions of the brain stem at higher levels virtually belong to the type which has a purely ascending axon, and that the dichotomizing type would not be affected. This may be true in adult animals. However, in very young animals, like those used here, the above assumption appears not to be tenable. First, the nerve cells are far more susceptible to damage to their axon the first days after birth than later.[7] Second, a comparison with the retrograde changes in the reticular formation following high lesions of the spinal cord (unpublished observations) is interesting. In such cases the number of normal giant cells left is so small that it does not equal the number of changed cells following brain stem lesions. It must be concluded, therefore, that some of these cells react to transection of either their ascending or their descending axonal branch; i. e., many of the giant cells at the level of the abducent nerve have, in addition to a long ascending branch, a descending axonal branch. That this type of reaction is not unique is learned from findings made recently concerning the efferent fibers from the red nucleus.[11] It cannot be decided whether the large, medium-sized, and small cells of the reticular formation having ascending and descending axonal branches behave in the same manner as the giant cells, but this does not appear unlikely. The demonstration that the ascending fibers from giant cells passing the mesencephalon are derived from cells projecting also in a caudal direction has important bearings on physiologic interpretations of the function of the reticular formation.

Topographic Aspects

Although the ascending reticular fibers have been shown to take origin at all levels of the brain stem, there are certain regions which are particularly rich in rostrally projecting neurons (Fig. 8). Furthermore, they are restricted to the medial two-thirds of the reticular formation. These topographic fea-

References 9, 10, 12, and 13.

tures raise some questions. First, it should be considered whether there is any correspondence with particular cell groups outlined by different authors in cytoarchitectonic studies. Since the most detailed and most recent studies of this type are those of Olszewski and collaborators,* reference will be made to their subdivision only. Even if their maps are from rabbit and man, comparison with the cat's brain is possible.

A comparison shows that there is relatively little correspondence. Thus, the area at the level of the abducent nerve, showing the maximum of changes, is part of Olszewski's nucleus reticularis pontis caudalis, but is restricted to its medial half only and to the middle third of its longitudinal extension. Furthermore, at bulbar levels, the degenerated cells are present in the subnucleus reticularis ventralis of the medulla oblongata, but only in its peripheral medioventral region. Its large dorsolateral part is free from changed cells. The area labeled *N. r. l.* (nucleus reticularis lateralis) in the rabbit atlas (not to be confused with the well-circumscribed nucleus to which this name is usually applied, also called the nucleus of the lateral funiculus †) also is the seat of considerable changes, but, again, not in its entirety, but only in its caudal part. On the other hand, changed cells are found throughout the nucleus reticularis gigantocellularis of Olszewski. The limitation of changes in the raphe nucleus of the medulla oblongata to its ventral part only (Figs. 2 and 4) appears to have no counterpart in the cytoarchitectonic maps. On the whole, therefore, the distribution of the perikarya of ascending neurons in the reticular formation does not lend support to the assumption that all subnuclei which can be outlined on a cytoarchitectonic basis represent particular functional units. Nevertheless, future studies may show that they deserve separation on the basis of other criteria.

The uneven distribution at different levels of the brain stem reticular formation of cells projecting rostrally can scarcely be considered as fortuitous. When one is attempting to understand the significance of this feature, it may be suggested as a working hypothesis that the relative density of such cells at different levels may bear some relation to sources of afferent fibers activating them. Various sources may be taken into consideration.

In recent physiologic studies, impulses of spinal origin are generally assumed to reach the reticular formation via collaterals from the specific long ascending fiber systems. Little information of such collaterals is to be found in the anatomic literature. Although degeneration has been observed by several students in the reticular formation in Marchi material following spinal cord lesions, this may as well be due to degeneration of direct spinoreticular fibers as to collaterals from other systems. Cajal [15] and Glees,[23] however, describe collaterals from spinal fibers ascending on the ventrolateral aspect of the medulla (spinothalamic and others) which appear to be given off chiefly at the medullary level. The fibers of the medial lemniscus, according to Cajal,[15] do not give off collaterals until they reach the pons, and the collaterals to the reticular formation appear to be sparse. Such collaterals are not mentioned, however, in some recent experimental studies of the medial lemniscus.

Direct spinoreticular fibers have been traced to the level of the sixth and seventh cranial nerves,‡ or even farther.[26] We have been able to confirm this in studies with silver methods [22] following lesions of the spinal cord (unpublished). However, it appears that the majority of the direct spinoreticular fibers terminate at lower medullary levels,§ as do also the collaterals of the spinothalamic fibers.‖

It appears from these data that probably the activation of the rostrally projecting neurons by impulses derived from the spinal cord will take place chiefly at lower medullary levels. Since, however, spinal impulses may

* References 36, 42, and 43.

† References 9 and 55.

‡ References 38 and 45.

§ References 37 and 38.

‖ References 15 and 23.

reach also higher levels, it is difficult to correlate the quantitative regional variations of ascending neurons at different levels with the spinoreticular influx.

More promising appears a consideration of other types of afferents, carrying impulses which, according to physiologic findings, have been shown to activate the ascending reticular formation. It will be realized that in the region around the abducent nerve there are important stations in sensory trigeminal and acoustic pathways. Collaterals to the reticular formation from the lateral lemniscus, described, among others, by Cajal [15] and Stotler,[54] have been discussed in physiologic studies as possible mediators of acoustic impulses to the reticular formation. However, at the levels where the lateral lemniscus ascends, there are relatively few neurons with ascending axons (for example, Drawings *1-3* in Fig. 4). The superior olive, however, is situated close to the maximal ascending projection area, and it is of interest that collaterals from the axons of its cells have been traced to the adjoining reticular formation in Golgi preparations,[15] as well as in experimental studies.¶ Possibly the nuclei of the trapezoid body and its fibers may also play a role in collateral activation of this part of the reticular formation.

Another nucleus situated at the level under consideration is the chief sensory nucleus of the trigeminus. Direct sensory trigeminal fibers have apparently not been traced to the reticular formation proper, although some of them, according to Torvik (unpublished data), reach the area intercalated between the nucleus of the solitary tract and the spinal fifth nucleus. However, collaterals from secondary trigeminal fibers from the chief, as well as the spinal, trigeminal nucleus pass to the reticular formation.# Whether they are more abundant from one of these sources is not known. The presence of an area of the reticular formation intercalated between the trigeminal nucleus and the site of rostrally projecting neurons may suggest that the latter may be activated via the former, this being chiefly a collection of interneurons.

Concerning the other maximal area of rostrally projecting neurons, at the level of the rostral third of the inferior olive, several sources of afferents may be considered. In addition to spinothalamic collaterals * or spinoreticular fibers,† the vagal afferents are of particular interest. While direct vagal root fibers cannot be traced to the reticular formation experimentally (Torvik, unpublished data), collaterals from the secondary ascending fibers from the nucleus of the solitary tract have been described.‡

Although not decisive, the data mentioned are compatible with the assumption that the concentration of rostrally projecting neurons at certain levels of the brain stem may be a reflection of the fact that these parts of the reticular formation are particularly important areas in the reception of impulses which have been shown in physiologic studies to activate the ascending reticular system.

The pathways for optic and olfactory impulses entering the ascending activating system are not known. It is of interest to note, however, that Cajal [15] describes collaterals to the mesencephalic reticular formation from cells of the fourth layer in the superior colliculus. From his Figure 129,§ it appears that they reach chiefly the medial part of the reticular formation.

In this study we have been concerned with the cells of the reticular formation proper only. However, it should not be overlooked that other groups of neurons situated within it, and appearing more or less clearly as particular nuclei, may also be concerned in the conduction of ascending impulses within the reticular formation of the brain stem. Thus, Niemer [41] observed cell loss in the dorsal tegmental nucleus of Gudden following lesions above this. We have not been able to recognize definite acute cellular changes in this nucleus, but this negative finding is not

¶ References 44, 47, and 54.

References 15 and 44.

* References 15 and 23.

† References 37 and 38.

‡ References *2* and 15.

§ Reference 15, Vol. II.

decisive. Nor does our failure to detect changes in the very small cells of the central (periaqueductal) gray matter exclude the possibility that it may in part project rostrally. Even if it has important descending projections to the inferior olive,[56] ascending fibers from different sources have been traced to the central gray matter.‖ Whether the cell group situated between the oculomotor root fibers and projecting rostrally (Fig. 6) is part of the ascending activating system cannot be decided. Finally, it should be recalled that, so far as our material permits conclusions concerning the course of the ascending reticular fibers, they are in agreement with those of other authors.¶ That some at least of the ascending fibers taking origin in the pons may course in the medial longitudinal fasciculus appears from findings made by Bucher and Bürgi,[14] and, according to Cajal,[15] the same is true for the axons of the large cells of the medullary reticular formation.

Functional Correlations

The findings made in this study make clear that the so-called ascending activating system is organized in a more complex manner than hitherto imagined. The impulses ascending within the reticular formation of the brain stem must be supposed to utilize the rather numerous ascending fibers demonstrated here. Shorter relaying neuronal circuits and complex intrareticular routes may also be involved, and may account for the prolonged activity recorded at higher levels following stimulation of the lower reticular formation.# It is clear, however, that the substrate of the ascending reticular activating system cannot be simply a series of short neurons, as has so far been generally assumed.

It is of interest to consider some of the physiologic findings in the light of the new data on the long ascending reticular fibers and their distribution. The situation of most of these neurons in the medial part of the brain stem is in agreement with the findings that only lesions of the medial areas of the reticular formation are followed by synchronization in the EEG and behavioral changes indicating lack of activation.* However, such effects, according to Bremer,[6] Lindsley and associates,† and French and Magoun,[18] are obtained only with lesions at the pontine-mesencephalic level, while more caudal lesions are negative in this respect. Furthermore, Rossi and Zirondoli [49] found that successive transections of the brain stem have a constant synchronizing effect on the EEG only when they are made just rostral to the level of the chief trigeminal nucleus. It is interesting to correlate these observations with the finding in this study that quantitatively a particularly important area of reticular neurons projecting rostrally is at the critical level determined in these experiments.

As discussed above, there is some anatomic evidence for the assumption that trigeminal, and particularly acoustic, impulses reach the activating system at this level. A lesion here, however, not only will eliminate these but will also prevent the rostral propagation of afferent influxes to the reticular formation at medullary levels. These impulses may be of vagal nature, but presumably others, not least spinal impulses, may be assumed to activate particularly the caudal part of the reticular formation. The direct spinoreticular fibers should be kept in mind in this connection. It appears quite likely that these fibers may be more important in the activation of the caudal part of the ascending reticular system than collaterals given off by the long sensory ascending pathways. However, the latter, in addition to acoustic, trigeminal, optic, and olfactory impulses, may be sufficient to maintain an appropriate level of activity of the ponto-mesencephalic part of the system, even if the medullary part of it is destroyed.

If it is right that the grouping of larger numbers of ascending reticular neurons at certain levels of the brain stem is related to the entrance of larger contingents of affer-

‖ References 21 and 57.

¶ References 37 and 50.

References 19 and 52.

* References 18, 30, and 31.

† References 30 and 31.

ents, some doubt may be cast on the assumption that there is no segregation of the reticular activating system with regard to the types of incoming impulses. Some findings of relevance may be mentioned. Thus, Ades and Brookhart,[1] in a study of the acoustic pathways, found that the superior olive discharges into the adjacent reticular formation. Furthermore, the studies of single-unit responses in the reticular formation are interesting. Several authors have demonstrated the presence of units responding to more than one kind of stimuli (Moruzzi [39]). However, in the recent study of Scheibel, Scheibel, Mollica, and Moruzzi [51] only few units were found which responded to acoustic as well as to other kinds of impulses. One wonders whether this may not be due to their recording only from the medulla, particularly since acoustic stimuli were regularly found to activate reticular neurons in the mesencephalon and upper pons by Amassian and De Vito.[3]

If we are right in taking the regional distribution of reticular neurons projecting rostrally as indicating the most potent areas of the reticular activating system, the assumption implies that this system is not as diffusely organized as hitherto assumed. Although present along the entire brain stem, it is particularly developed at certain levels. It appears to overlap and coincide more or less with the inhibitory, and particularly with the facilitatory, area,‡ as physiologically determined; but even these systems may have more circumscribed maximal representations within the brain stem reticular formation. This assumption is supported by our preliminary finding that the caudally projecting neurons, although present over wide areas of the reticular formation, have sites of predilection which differ to some extent from those of the ascending neurons.

The opinions expressed above must be considered as suggestions. They may, however, serve some purpose as working hypotheses, which may stimulate more detailed studies of the reticular activating system, by physiologic as well as anatomic methods. Not least among the latter, studies by the Golgi method, undertaken with due reference also to regional features, may prove fruitful.

‡ References 34 and 48.

SUMMARY

The distribution of retrograde cellular changes occurring in the reticular formation of the medulla, pons, and mesencephalon following lesions at different levels of the brain stem has been studied in young kittens (modified Gudden method [8]).

Characteristic retrograde changes occur in all types of cells (giant, large, medium-sized, and small) in the reticular formation. These changes are taken as evidence that the affected cells have axons projecting rostrally. Only cells presenting the fully developed picture of these changes have been taken into account.

Although distributed along the entire length of the medullary, pontine, and mesencephalic reticular formation, the neurons having ascending axons are restricted to the medial two-thirds of the reticular formation. They are particularly abundant at the level of the rostral third of the inferior olive and at the level of the abducent nerve. Rostrally projecting giant cells are present only in the latter area. Some cells of the ventral part of the raphe nucleus of the medulla and pons are also changed.

Homolaterally ascending fibers predominate. It is estimated that in the maximally affected areas approximately one-third of all giant, large, and medium-sized cells have an ascending axon. Concerning the smallest cells numerical estimates cannot be made. It is possible that the number of ascending fibers from cells of this type is appreciably larger than is shown by use of the present method. The contribution from the mesencephalon may, therefore, be greater than appears from our findings.

A considerable proportion of all neurons projecting rostrally have long axons which pass beyond the mesencephalon. Whether there are also shorter ascending axons cannot be decisively stated, but it appears likely. Evidence is produced that some of the giant

cells projecting rostrally are of the type that is provided with axons dichotomizing in an ascending and a descending branch.

The presence of a considerable number of reticular neurons possessing long ascending axons demonstrates that the ascending activating system cannot be considered as a system of short neuronal relays only. The aggregations of cells with long ascending axons at certain levels of the brain suggest a relation to the entry of afferents influencing the activating system. Anatomic information bearing on this subject is discussed.

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Effects of Diphenylhydantoin (Dilantin) on Adrenal Cortical Function

A Study in Nonepileptic Human Subjects

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The importance of an adrenocortical component in various human and experimental convulsive states has recently been reviewed (see these articles for complete bibliography). Convulsive seizures have responded to treatment with desoxycorticosterone (DCA) in certain instances. On the other hand, both cortisone and corticotropin (ACTH) have exacerbated experimental seizures or induced more abnormalities in the electroencephalograms of epileptics. These hormones also have induced electroencephalographic changes in varying degree and/or convulsions in previously seizure-free human subjects. It has been shown that endogenously or exogenously increased adrenocortical hormone levels may predispose to greater convulsive susceptibility or lowered electroshock threshold in experimental animals.

Recently, Staple [6] found that diphenylhydantoin (Dilantin) produced degenerative lesions in the adrenal cortex of rats. He has suggested that this drug might exert its anticonvulsant effect by decreasing adrenal cortex activity. However, Woodbury [7] concluded from his own experiments that diphenylhydantoin stimulated the adrenal cortex, especially during acute administration.

On the basis of these observations, it was felt that a control investigation of the effect of diphenylhydantoin on the adrenocortical activity of nonepileptic human subjects would be of some interest and necessary prior to any investigation in epileptics.

METHODS AND PROCEDURE

The 12 patients used in this study were from the rehabilitation ward of the Grace-New Haven Community Hospital. The patients selected were all in a "basal" state, on normal diets and adequate fluid intake. Nine of the patients were postpoliomyelitis rehabilitees; one was recovering from a cerebrovascular accident; one had had a spinal cord injury, and one was recovering from coronary thrombosis. These patients had never experienced seizures of any type. Hospitalized subjects were chosen to facilitate drug administration and urine collections, since it was felt that this would be impractical on an outpatient basis. Variations due to environment, diet, stressful situations, and activity were minimized in this group of subjects, treated almost totally alike in the hospital.

Each subject served as his own control. Prior to drug administration, basal excretory levels of both urinary 17-ketosteroids and corticoids were determined as indices of adrenocortical activity. The 17-ketosteroids were estimated according to the method of Holtorff and Koch [8] with several modifications.[9] Corticoids were estimated according to the method described by Gornall and MacDonald.[10] All determinations were performed on 24-hour urine samples.

Control urinary values for these indices were determined over a four-day period in all cases. Sodium diphenylhydantoin was given orally in

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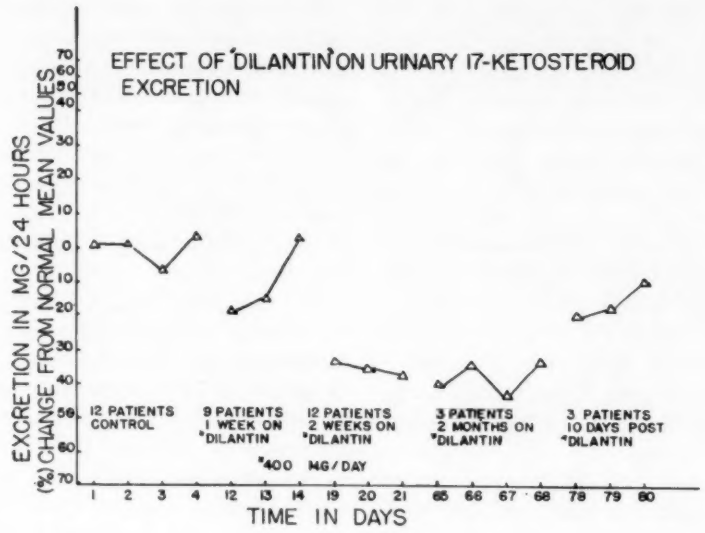
EFFECT OF 'DILANTIN' ON URINARY 17-KETOSTEROID EXCRETION
EXCRETION IN MG/24 HOURS (%) CHANGE FROM NORMAL MEAN VALUES
12 PATIENTS CONTROL
9 PATIENTS 1 WEEK ON 'DILANTIN
12 PATIENTS 2 WEEKS ON 'DILANTIN
3 PATIENTS 2 MONTHS ON 'DILANTIN
3 PATIENTS 10 DAYS POST 'DILANTIN
'400 MG/DAY
TIME IN DAYS

Figure 1.

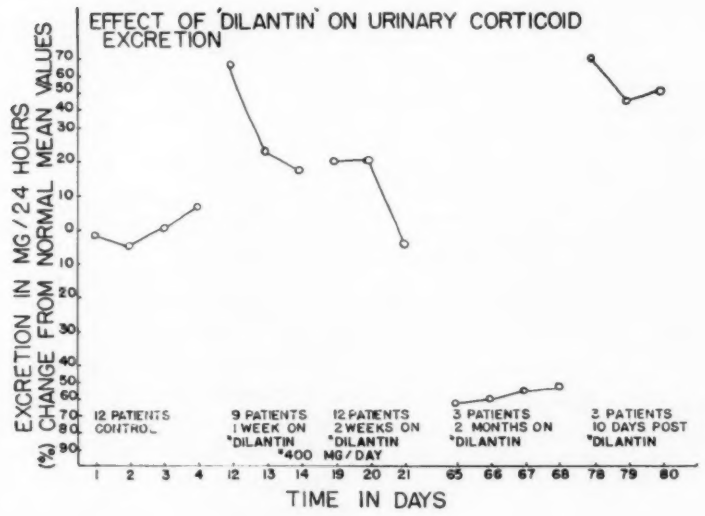
EFFECT OF 'DILANTIN' ON URINARY CORTICOID EXCRETION
EXCRETION IN MG/24 HOURS (%) CHANGE FROM NORMAL MEAN VALUES
12 PATIENTS CONTROL
9 PATIENTS 1 WEEK ON 'DILANTIN
12 PATIENTS 2 WEEKS ON 'DILANTIN
3 PATIENTS 2 MONTHS ON 'DILANTIN
3 PATIENTS 10 DAYS POST 'DILANTIN
'400 MG/DAY
TIME IN DAYS

Figure 2.

divided doses, totaling 400 mg. per day. Administration of the drug was maintained in all subjects for about three weeks, at which time nine discontinued it. However, three patients carried on for over two months. Urine collections were obtained at varying periods during the drug administration, as shown in Figures 1 and 2. The three patients were followed for post-drug-excretion values, 10 days after the cessation of administration.

Thus, the excretion of 17-ketosteroids and corticoids was determined prior to diphenylhydantoin administration, one week after the initiation of the drug, two weeks following this, and, with three patients, two months afterward.

RESULTS

The results obtained have been summarized in the accompanying Table and graphically represented in Figures 1 and 2. Data from all of the patients have been averaged and combined, and finally expressed in terms

of the percentage changes from normal mean values (control levels). The excretion patterns for 17-ketosteroids are shown in Figure 1, and the corticoid excretions, in Figure 2. Diphenylhydantoin had a variable effect upon 17-ketosteroid excretion, after one week of administration; however, after two weeks the excretion levels were well below control values. This decrease in 17-ketosteroid excretion persisted in the three patients who took diphenylhydantoin for two months. It will be noted that in the three subjects who were followed 10 days after cessation of diphenylhydantoin, the 17-ketosteroid excretion level had not as yet returned to predrug value.

After one week of drug administration urinary corticoid excretion had increased. After two weeks the corticoid excretion still was greater than control levels; however, after two months, corticoid excretion was markedly depressed. Ten days after the cessation of diphenylhydantoin, corticoid excretion values rebounded to levels well above normal.

*Average Excretion Values (All Patients) in Each of the Study Periods**

	17-Ketosteroid Excretion				Corticoid Excretion			
	Day of Determination				Day of Determination			
Study period	1	2	3	4	1	2	3	4
Control on diphenylhydantoin	10.7	11.3	10.6	11.2	2.0	1.8	2.1	2.2
1 wk	7.8	9.8	11.1	....	3.4	2.4	2.3	...
2 wk	7.1	6.7	6.5	....	2.4	2.4	1.9	...
2 mo	5.6	7.1	6.8	7.0	0.7	0.7	0.8	0.9
After diphenylhydantoin								
10 days	7.4	7.2	8.3	....	3.4	2.9	3.0	...

* As shown in Figures 1 and 2. Values are expressed in milligrams per 24 hours.

COMMENT

In the present study it was found that there was an initial increase in urinary corticoid excretion levels, followed ultimately by a significant depression and similar, but less marked, changes in the 17-ketosteroid excretions. These results suggest that diphenylhydantoin has a primary stimulatory effect upon the adrenal cortex, followed by a secondary, and probably prolonged, depressant action if drug administration is maintained. The finding of an initial stimulatory effect is in agreement with Woodbury.[7] Staple [6] had previously reported, however, that continued diphenylhydantoin administration caused degenerative changes in the adrenals of animals. He inferred from this that diphenylhydantoin is probably an adrenal cortex depressant, and that this effect might explain the mode of action of the drug in controlling human convulsive seizures.

Recently Bray, Ely, and Kelley [5] reported the inability of human epileptics, on chronic diphenylhydantoin administration, to respond to corticotropin with increased adrenocortical activity. They found that normal persons not receiving diphenylhydantoin responded to corticotropin administration with a sharp rise in plasma corticoids, while the epileptics taking diphenylhydantoin responded to corticotropin administration with an insignificant increase in plasma corticoids. Thus, they concluded that diphenylhydantoin may stimulate the adrenal cortex initially but will produce in time a state of relatively diminished adrenocortical responsiveness. These findings are in accord with those of the present investigation.

Although the mode of action of diphenylhydantoin in controlling human grand mal seizures is still unsettled, it is conceivable that its depressant effect on the adrenal cortex in long-term therapy may be an important mechanism. This consideration of a possible role of the adrenal cortex in convulsive states does not in any way minimize the main role of the central nervous system in convulsive activity, but it does point to a

different approach related to general bodily physiology. It is important to note that no patient taking diphenylhydantoin over a long time has been observed or reported to have developed significant signs or symptoms of adrenal cortex insufficiency. Yet, the present findings indicate that under the chronic influence of diphenylhydantoin, the adrenal cortex may be operating at lower levels of physiological efficiency.

SUMMARY

Diphenylhydantoin (Dilantin) was administered orally for varying periods of time to 12 nonepileptic human subjects and their adrenocortical activity was estimated by measurements of urinary excretion of 17-ketosteroids and corticoids. During acute administration of the drug 17-ketosteroid excretion remained essentially unchanged, but the corticoid excretion increased; during prolonged administration the excretion of both decreased significantly. These findings suggest that diphenylhydantoin may have an initial stimulatory and a later depressant action on the adrenal cortex. The implications of the results are discussed with regard to convulsive states in general and the mode of action of diphenylhydantoin as an anticonvulsant.

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Language Disturbances in Cerebral Disease

Concept of Latent Aphasia

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The purpose of this communication is to report the findings of a comparative study of the pattern of intellectual functioning in groups of senile and arteriosclerotic patients. The results of this investigation raise the question of the existence of an aphasic disorder of subclinical intensity in certain types of cerebral disease.

Most psychometric instruments which are currently utilized for the measurement of intellectual impairment in cerebral disease are based upon the principle of a differential decline of abilities coincident with either advancing age or cerebral pathology.* Specifically, it is believed that verbal abilities, as assessed by vocabulary level or range of information, are likely to be better preserved than are abilities involving immediate memory, visual analysis and synthesis, and abstract reasoning capacity.

There is considerable empirical evidence which supports this principle. Nevertheless, certain qualifications must be noted. First, it is obvious that the principle holds only for "nonaphasic" cerebral disorder. Secondly, if a severe behavioral disorganization occurs as a consequence of cerebral disease, it is likely to be characterized by a significant decline in all abilities, verbal as well as nonverbal, which tends to obliterate any discrepancy in performance level on the two types of tasks. Finally, there is considerable disagreement as to whether the differential changes in abilities which are observed in the normal ageing process are in fact essentially similar to those found in intellectual impairment associated with cerebral disease.

In 1941, Shakow, Dolkart, and Goldman,[6] studying the senile and arteriosclerotic dementias, found that vocabulary level in both groups of patients was significantly inferior to that of normal subjects of comparable age, and they posed the question of whether a "generalized aphasic difficulty" might not be characteristic of these patients. However, further analysis of their findings shows that while the two groups of patients were similar with respect to vocabulary level, the senile dements were much inferior to the arteriosclerotic patients with respect to performance level on tasks involving recent and remote memory.

On the basis of these observations, we thought it would be of interest to compare groups of senile and arteriosclerotic patients, utilizing both a vocabulary test and a nonverbal intelligence test, to determine whether differences in performance pattern exist.

PROCEDURE

Patients were assigned to membership in the two groups on the basis of the established diagnosis and the results of a supplementary clinical examination particularly designed to disclose the presence of arteriosclerosis. All patients who showed aphasic symptomatology on clinical examination, whose impairment was so severe that only chance success was achieved on the psychologic tests, who had cortical atrophy as determined by pneumoencephalography, or who suffered from disease of syphilitic origin were excluded from consideration.

The two diagnostic groups, as finally constituted, consisted of 27 arteriosclerotic patients (mean age, 65.22 years; mean duration of hospitalization, 21 months) and 25 senile dements (mean age, 73.08 years; mean duration of hospitalization, 20 months). All patients had been residents of Paris or its environs for several years. Socioeconomic status of

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* References 1 through 5.

the groups was about average, the majority of the patients having been skilled workers, civil servants, or tradesmen. None came from the learned professions. The Vocabulary test of Binois and Pichot [8] and the Progressive Matrices test (1938 edition) of Penrose and Raven [7] were given to the patients. The first test, in the form in which it was given, is of the same type as the Binet or Wechsler-Bellevue vocabularies; i. e., the patient is requested to define words, and his response is counted as correct if he can indicate in one way or another that he knows the meaning of the word. The second test is a nonverbal task requiring both reasoning and visuoanalytic abilities. It is considered to be an excellent measure of efficiency of intellectual function and has the added advantage that a standardization with respect to age (up to 70 years) has been provided by Foulds and Raven.[8]

RESULTS

The findings are presented in the accompanying Table. It will be noted that the vocabulary level of the arteriosclerotic patients was decidedly lower than that of the senile patients. The obtained difference of 8.26 points in score is highly significant ($p = 0.001$).

Test Performances of Senile and Arteriosclerotic Patients

Test	Senile (N-25)	Arteriosclerotic (N-27)	Diff.	p
Vocabulary	Mean 26.00 S. D. 6.27	Mean 17.74 S. D. 7.05	8.26	<0.001
Progressive Matrices	Mean 15.96 S. D. 3.67	Mean 14.07 S. D. 4.88	1.89	>0.10

On the Progressive Matrices test the senile patients obtained a mean score of 11.24, while the mean score of the arteriosclerotic patients was 14.07; i. e., the arteriosclerotics appeared to be superior in efficiency of intellectual function despite the lower vocabulary test score. However, since the age norms of Foulds and Raven go up only to age 70 and the mean age of the senile patients was 73 years, a direct comparison of the two means did not appear to be justified and the possibility arises that the observed difference in pattern of performance (vocabulary level *vs.* nonverbal intellectual level) might be a function of the difference in age rather than of diagnostic category. To take account of this difference in age, the finding of Foulds and Raven that there is a loss of about 3 points in score for each 5 years of age was utilized to correct the scores of the senile patients. Since the difference in age between the two groups was 7.86 years, multiplication by $\frac{3}{5}$ yielded an indicated correction in score of 4.72 points to be added to the mean Progressive Matrices score of the senile patients. The corrected score was 15.96, which was not significantly different from the mean score for the arteriosclerotic patients. Thus it appeared that this correction did not significantly alter the observed performance patterns. The arteriosclerotic patients did not differ from the senile patients with respect to general intellectual efficiency but did show a marked inferiority in vocabulary level.

The difference in the psychometric patterns of the two groups of patients can be expressed by calculating the discriminant function between the two groups.† If X_1 is Progressive Matrices score and X_2 is Vocabulary test score, the discriminant function is

$$y = X_1 - 0.75X_2$$

In establishing the discriminant score, y_0, in such a way as to minimize errors in classification, one obtains:

$$y_0 = 63.75$$

Under these conditions the error of classification between the senile and the arteriosclerotic patients is 13.5%. Of course it is realized that the magnitude of this maximal value is dependent in part upon sampling fluctuation and that cross validation would probably yield a somewhat lower predictive efficiency.

COMMENT

The findings indicate that distinctive patterns of psychologic test performance are shown by arteriosclerotic patients as compared with patients with senile dementia. The latter group show a pattern of test performance (high vocabulary level *vs.* low

† References 9 and 10.

spatial reasoning ability) which is in accord with expectations. But the arteriosclerotic patients also show a specific and rather striking decline in vocabulary level. It is noteworthy that these patients were "non-aphasic" by the usual clinical criteria.

We are inclined to advance the following interpretation of these findings. The two groups of subjects studied suffer from the same degree of basic intellectual impairment, as measured by performance on the Progressive Matrices test. In senile dementia, the decline in vocabulary level, if it exists, is due solely to general intellectual impairment.‡ In arteriosclerotic dementia, on the other hand, a much more striking decline in vocabulary level is observed, which is due not only to the factor of general intellectual impairment but also to a supplementary specific language impairment. Since all patients in the two groups who presented aphasic symptoms were excluded from consideration, we propose to give this specific language impairment the designation of "latent aphasia."

This hypothesis receives indirect support from the long-standing clinical observation that aphasia is only uncommonly encountered in senile dementia, while it is a frequent occurrence in arteriosclerotic dementia. The results of the present study suggest that practically all arteriosclerotic dements show a certain degree of aphasia, which is manifested clinically only in a small proportion of cases but which is demonstrable by psychologic test methods.

Anatomical findings are also consistent with the hypothesis. In senile dementia the cortical lesions are generally diffuse, while in arteriosclerotic dementia the lesions are likely to be localized predominantly in the temporo-occipital regions. This difference in localization of lesions appears related to the symptomatology, and the observed latent aphasia may be viewed as a focal symptom in cerebral arteriosclerosis.

The concept of latent aphasia may be fruitfully applied to other disorders, e. g., epilepsy. Impoverishment of vocabulary in epileptic dementia is a clinical observation of long standing (Ziehen, Ranschburg, Hart and Spearman). In 1933, Simmins,[11] comparing the test performances of hospitalized epileptics and of other patients, was impressed by the marked inferiority of the epileptic patients and concluded that they showed a "specific verbal disability." Similar observations have been made by later authors, such as Capps.[12]

A number of criticisms have been leveled against an interpretation of this finding as a distinctive epileptic phenomenon. It is pointed out, for example, that from a clinical point of view it is difficult to conceive of a specific "epileptic" dementia. Epileptic dementia exists, of course, but such cases can have widely different etiologies (e. g., trauma, neoplasm), and both the dementia and the epilepsy may be considered to be consequences of the same underlying determinant. The only cases which can be considered to show a relatively specific dementia are those idiopathic cases which have frequent and repeated attacks leading to irreversible cerebral lesions through the mechanisms of hemorrhage and asphyxiation. Progress in anticonvulsant therapy has made this type of case increasingly rare.

A more important criticism of a specifically "epileptic" interpretation of the finding of language impoverishment is that the disorder often involves an interruption of both academic instruction and social interaction and that it is this educational and cultural impoverishment which accounts for the poor language development. This hypothesis has strong empirical support. Davies-Eysenck,[13] utilizing a vocabulary test and the Progressive Matrices test, studied the development of epileptic children over a period of two years through a test-retest technique. She found that those children who attended school

‡ Because of the lack of appropriate age norms, it cannot be stated with certainty that the senile patients do show a decline in vocabulary level. However, the findings in analogous investigations by other authors make it extremely probable.

in spite of the seizures showed a normal vocabulary development, while those whose school attendance had been interrupted showed a retardation in vocabulary development. That this was not a general retardation in intellectual development was indicated by the finding that there was no significant difference in Progressive Matrices test performance. My personal observations on a group of 150 adult epileptic patients also support this idea. Regardless of etiology (traumatic, encephalitic, idiopathic), a definite negative relationship between vocabulary test performance and age of onset of convulsions was found.

But it is possible that still another factor, that of latent aphasia, may enter the picture. The importance of temporal localization in aphasic symptomatology and the high frequency of temporal epilepsy among hospitalized epileptic patients [14] raise the question as to whether a certain proportion, at least, of those epileptics who show language disturbances are not suffering from a latent aphasic disorder. There is some evidence to support this idea. Rey,[16] utilizing the Progressive Matrices and the Mill Hill vocabulary test, found that the psychometric pattern defined by the verbal score being inferior to the nonverbal score appeared to be characteristic of subjects who showed temporal EEG dysrhythmias. Similarly, Foulds § observed an analogous psychometric pattern in epileptics with temporal and parietal EEG abnormalities.

It must be admitted that, at the present time, there is no strong evidence to support the hypothesis that latent aphasia is a factor in producing the verbal impoverishment so often noted in epileptics. The two studies which have been cited can be considered as only suggestive in this regard, and continued investigation of the problem is indicated.

Further evidence for the idea that latent aphasia may be a fruitful concept in the interpretation of the test performances of patients with cerebral disease is provided by the recent study of Heilbrun.‖ This author found that nonaphasic patients with left hemisphere lesions showed a test performance pattern which was significantly different from that of patients with right hemisphere lesions, the former showing a lower verbal test level as compared with nonverbal test level and the latter showing the opposite pattern.

In summary, it is suggested that in arteriosclerotic dementia, and probably also in a certain proportion of epileptic cases, the striking decline in vocabulary level which is observed is related to the presence of localized cerebral lesions causing a mild aphasic state which may escape clinical detection by gross clinical observation but which manifests itself in a characteristic pattern of psychologic test performance. It is probable that this relationship also holds for other organic defect states.[18] This possibility indicates that one must be extremely cautious in designating "typical" test performance patterns in cerebral disease, and it emphasizes the necessity for further investigations of homogeneous groups of patients. From the observations which have been reported it seems evident that the assumptions underlying the application of many so-called deterioration scales are in need of revision.

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Statistical Control Studies in Neurology

VI. Bell's Phenomenon

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According to Majoros,[1] Soemmerring described upward movement of the eyeballs with closure of the lids in 1801, prior to Bell's [2] publication of 1823. However, since Bernhardt's [3] suggestion of 1898, Bell's name has been associated with this sign. It will most likely continue to be known as Bell's phenomenon and will be so designated in this study.

The presence or absence of this sign may be of clinical value. Thus, Margulièss [4] stated that the absence of Bell's phenomenon can be used to distinguish hysterical from organic facial paralysis. Bielschowsky [5] emphasized that the intactness of this sign with the absence of upward movement of the eyeballs on voluntary gaze differentiates a supranuclear from a nuclear lesion in the brain stem. However, in view of the absence of Bell's phenomenon in many patients with no known neurologic disorders, two large series, one of patients and one of healthy people, were studied to obtain the frequency of Bell's sign and to determine whether its absence can be correlated with other factors, such as age and neurologic findings.

With only a few exceptions, the literature contains reports of small numbers of persons tested for Bell's phenomenon. Thus, Teitelbaum [6] found upward movement in all of 14 normal people. Slotopolsky [7] examined 33 healthy people; 25 had upward movement of the eyeballs. Granström [8] found upward movement in 75, downward movement in 6, varying movement in 1, and absence of movement in 1 of 83 normal people. Von Michel [9] and Fumarola [10] indicated that absence of Bell's phenomenon occurs only rarely; unfortunately, the number of persons examined and the exact figures were not given. Abraham [11] stated that "one should bear in mind that practically all normal individuals show [typical] Bell's phenomenon." Köster [12] wrote that he observed Bell's sign in "hundreds of healthy people."

Hall [13] examined 1250 people, mostly adults. Many were in normal health. Others had presented themselves for some illness, but in none was it due to organic nervous disease. The first 400 cases were not included in his percentages, since he was developing the technique for the test. Hall found upward maximal movement in 477 cases (59.6%), upward medium movement in 230 (28.8%), and absence of upward movement in 93 (11.6%).

METHODS AND MATERIALS

In the present investigation two groups of persons were tested for Bell's phenomenon. Group 1 was composed of 1264 hospital patients, admitted with no neurologic condition and ranging from 10 to 93 years of age; 653 were female and 579 male. Group 2 was composed of 1001 male draftees between the ages of 18 and 38.

The technique employed in the test was that of Hall. "The observer rests one hand on the forehead, presses the forefinger lightly but firmly on one upper lid so as to fix it and then asks the person under observation to shut his eyes. The extent and direction of movement of the uncovered eyeball is noticed together with the position ultimately reached. The eyelid is held up for a shorter or longer period of time and any further movement of the eyeball noted. The person is then told to open his eyes again. The same process is repeated with the other eye. In cases where there is doubt about the result, the investigator asks the person to close his eyes as before, without touching them at all. When the eyes are lightly closed, one lid is quickly lifted up and it is easy to see whether the eyeball is in the same position as it was in the previous experiment. If so, it is probable that this is the normal

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physiological position of rest. If the two positions are different, further examination is necessary to see which of either of the two is the natural position." Bernhardt [3] and Slotopolsky [7] favored forceful closure of lids in testing for Bell's sign; Köster [12] and Kestenbaum [14] favored light lid closure. In the present investigation Bell's sign was frequently demonstrated with light lid closure; moreover, in many instances it disappeared with forceful lid closure.

In the present study each eye was tested individually and then the two eyes were tested together. No significant difference was found between testing each eye separately and the two together. The only value of testing the eyes simultaneously is that only then can it be noted whether there is convergence, or divergence, or a conjugate position of the eyeballs. In the present series the divergent position of the eyeballs was the commonest, as was also found by Slotopolsky.[7]

RESULTS OF STUDY

Results in the hospital series, Group 1, are shown in the accompanying Table.

Incidence of Bell's Phenomenon in Hospital Series

Age Group	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
Total no. in age group	127	142	157	199	246	234	129	28	2
No. with absent Bell's sign	6	7	6	24	35	88	58	17	1
Per cent with absent Bell's sign	4.7	4.9	3.9	12	14.2	37.5	45	60	50

Thus, the incidence of Bell's sign in the entire hospital series was 19.14%. It was absent in 19.17% of the male and in 19.27% of the female patients. This confirms Hall's statement of no difference in the incidence in the sexes. The present series shows an increase in the absence of the sign with increase in age. Thus, it was absent in 6.9% of patients below 50 years of age and absent in 31.1% of those 50 or over. It was absent in 23.17% unilaterally and 76.97% bilaterally of the entire series.

In Group 2 it was absent in 5.7% of the entire series. In Group 1, of patients between 18 and 38, it was absent in 4.1% of the patients. Downward movement was demonstrated in only one of the draftees. Wilbrand and Saenger [15] stated that in only a small per cent of people do the eyeballs go down. Coppez [16] found downward movement in 2 of 200 normal cases. Granström [8] noted reversal from upward to downward movement with forceful closure of the lids in 12 of 83 healthy people. In the present investigation, although with forceful closure the range of upward movement was at times diminished, no reversal to downward movement was observed.

In view of the association of ocular phenomena and the tendon reflexes, as in Adie's [17] syndrome, a possible similar association between Bell's phenomenon and the ankle jerk was investigated. In the draftee series there were seven with unilateral and one with bilateral absence of the ankle jerk. Except for bilateral absence of Bell's phenomenon in one person with unilateral absence of the ankle jerk, Bell's phenomenon was intact in the remaining six. In the hispital series there were 271 patients with absence of the ankle jerk and with intact Bell's sign and 103 with absence of the ankle jerk and absence of Bell's phenomenon. From the data, it appears that there is no relationship between absence of ankle jerk and Bell's sign.

Various suggestions have been proposed as a basis for Bell's phenomenon. Fleischer[18] and Lauber [19] were of the opinion that it is a reflex resulting from pressure of the hard tarsus on the cornea. However, Coppez [16] showed that cocainization of the cornea does not alter Bell's sign. Another explanation offered is that Bell's phenomenon is the position of rest of the eyeballs when the desire to see is not present (Bell,[2] Bonnier,[20] Teitelbaum,[6] Dutoit [21]). Hall, supporting this view, states, "In actual life during the greater part of the waking hours the eyes are directed either at or below the horizontal plane and to a much less extent upwards." Hence, upward is the position of rest for the eyeballs. Abraham [11] considered Bell's sign to be an "instinctive reflex." Poos [22] believed that Bell's phenomenon is necessary to keep the flow of tears in close contact with the cornea while the patient is asleep or when

the eyes are closed. Wilbrand and Behr [23] accepted Bell's phenomenon as an associated movement with closure of the eyelids. Kestenbaum [14] stated that it is a kind of automatic compulsory co-movement and is a flight from the light. Slotopolsky [7] considered Bell's phenomenon as existing in two situations: one, with "lowering of general tonus of muscles occurring in fainting, dying, beginning of narcosis"; and the other, in which it is an associated movement with willful desire to close the lids. The present investigator favors the view that Bell's phenomenon is an associated movement occurring with closure of lids.

SUMMARY AND CONCLUSIONS

Bell's phenomenon was investigated in two groups of people: Group 1 was composed of 1264 hospital patients admitted with no neurologic disorders and varying in age from 10 to 93, and Group 2 was composed of 1001 male draftees from 18 to 38 years of age.

Bell's sign was not found in 19.14% of Group 1. Bell's sign was absent in 5.7% of Group 2. It was absent in 4.1% of the persons between the ages of 18 and 38 in Group 1.

Age appears to be a factor. Thus, Bell's sign in Group 1 was absent in 6.9% of the patients below 50 years and absent in 31.1% of those 50 and over.

Sex is not a factor.

There is no association between absence of Bell's phenomenon and absence of the ankle jerk.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Benjamin Boshes, M.D., *President*
Regular Meeting, March 8, 1955

Etiological Coexistence of Erythroblastosis Foetalis and Retrolental Fibroplasia in Oligophrenia. Dr. Samuel J. Lipnitzky.

Since H. Selye introduced the idea of the "adaptation syndrome," and Roger J. Williams, his concept of "genetotrophic disease," biochemical geneticists are adding almost daily something new to our scientific knowledge of the role played by heredity and environment in the development of neuropsychiatric conditions. The investigation done by a British molecular biologist, F. H. C. Crick, and others in the field of chromozomal constituents and their functions (proteins, deoxyribonucleic acid [DNA] and ribonucleic acid [RNA], etc.) may serve as an example of the latter. Many a neuropsychiatric condition which has been thrown into the wastebasket of medical ignorance, slowly but surely is being recognized and better understood for what it is. The point in question is the report of a 6½-year-old white boy whose mother was Rh-negative and whose father was Rh-positive. There was a history of other premature children and of a miscarriage prior to this past pregnancy. Because of various complications, the child's state of health at birth was such that, among other things, he had a blood transfusion and was placed in an oxygen tent for 10 weeks. Shortly afterward a diagnosis of retrolental fibroplasia was made. He is blind; his speech is very defective; he walks on his toes, and psychologically he functions on the level of a mental defective.

DISCUSSION

Dr. Douglas N. Buchanan: I should like to make two points. First, I do not believe it is yet universally accepted that excessive oxygen is the sole cause of retrolental fibroplasia. Second, in the paper as read, there was no mention that the child really did have erythroblastosis foetalis.

Cephalometric Studies of Interest to Neurologists. Dr. Samuel Pruzansky.

Cephalometric roentgenography is a means for obtaining quantitatively accurate measurements of the head from x-ray films. This technique permits the valid comparison of measurements or tracings derived from one film with those from another obtained in the same standardized procedure. It has been applied in the serial study of the growth of the head and, more recently, in the study of infants with various congenital abnormalities of the head.

The superposition of successive tracings of an infant with craniostenosis, on whom serial records were available from 1 month to 2 years of age, revealed that the regularity and steadiness of the growth process of the cranium was disturbed. Following craniectomy, the pattern of growth simulated the normal. As the coronal suture began to recalcify, the growth behavior reverted to its previous abnormal pattern. The significance of these findings as a diagnostic sign was discussed.

Congenital Midline Dysplasia of the Scalp. Dr. Paul R. Rosenbluth and Dr. H. F. Grossman.

Congenital scalp defects occur most frequently in the parietal midline. The lesions are usually oval and appear punched out. Abnormal vascular channels may communicate with dural sinuses in the region of the defect. The central area of skin is thin, and often necrotic. Fat, sweat glands, hair follicles, and connective tissue fail to develop normally.

These scalp defects may be mistaken for obstetrical trauma or encephalocele, but they are considered to be lesser variants of the ectodermal dysplasias in the dorsal midline of the developing fetus, such as meningocele and encephalocele.

The lesions heal spontaneously when small, but may result in meningeal infection or erode into the dural venous sinuses, with resultant hemorrhage. Treatment, medical and surgical, should be directed toward prevention of these complications.

DISCUSSION

DR. P. R. ROSENBLUTH (by invitation): The scalp has been rotated to cover the lesion. If healthy granulations could be started in this area, it might be possible to skin-graft the area.

Reflections on the Pathogenesis of Convulsive Seizures. DR. H. H. MERRITT (by invitation), New York.

PHILADELPHIA NEUROLOGICAL SOCIETY

Axel K. Olsen, M.D., *Presiding*

Regular Meeting, Feb. 4, 1955

Cortical Blindness: Report of a Case. DR. LEO MADOW.

Blindness due to lesions of the occipital lobes, so-called cortical blindness, is a rare condition, and few pathologically verified reports have been recorded. In this paper another case, confirmed at autopsy, was reported, and the clinical and pathological features were described.

A 45-year-old coal miner with silicotuberculosis suddenly went blind while in a delirious state. He had the classical symptomatic triad of cortical blindness, including complete loss of vision, pupillary reaction to light, and normal ophthalmological examination. The blindness persisted until his death. Pathological examination revealed arteriosclerosis of the cerebral blood vessels with hemolyzed blood in both posterior cerebral arteries. There was softening of the occipital lobe bilaterally, with destruction of both the gray and the white matter, chiefly the subcortical occipital white matter and the medial and inferior portions of the gray matter. These findings appear to substantiate the studies of Shellahear and others that the occipital pole frequently receives an anastomotic supply from the middle cerebral artery and that a posterior callosal branch of the anterior cerebral artery may anastomose with the posterior cerebral artery to supply the calcarine fissure medially.

DISCUSSION

DR. J. C. YASKIN: This paper is a good presentation, with a clear pathological description of the autopsy findings. I would like to ask one question. What caused the occipital softenings in this 45-year-old man? This topic recalls to mind three personal cases: In the first case a diagnosis of hysteria was made by three competent ophthalmologists. A supraclavicular node was palpated, and further search disclosed carcinoma of the stomach. Autopsy showed bilateral metastatic occipital lesions. The second case was that of a woman who complained of headaches and blindness and had slight papilledema, with no optic atrophy. Autopsy revealed bilateral meningioma involving the occipital lobe. A third case was that of a man who was diabetic, alcoholic, and syphilitic. He suffered from sudden blindness. Spasm of the basilar artery was suspected. Autopsy revealed a fresh thrombosis of the basilar artery. Bilateral blindness should always make us think of basilar artery thrombosis.

DR. C. RUPP: Pathologically proved cases of cortical blindness are rare. At the Philadelphia General Hospital we see one case about every 18 months. The diagnosis is often unsuspected, and the condition is very frequently thought to be hysterical blindness.

DR. ARTHUR B. KING: I have seen three cases of cortical blindness due to ventriculography, with hemorrhages into the occipital lobes, proved in one case and suspected in the others. In two of the cases the condition cleared completely.

DR. E. A. DENBO, Camden, N. J.: Recently I had a case of temporary cortical blindness, due to toxic encephalitis associated with an overwhelming pneumonia in a 2½-year-old child. An air encephalogram revealed marked cortical atrophy. One must be extremely careful not to give a hopeless prognosis of irrevocable visual loss in such cases.

DR. W. KELLY: I saw this case of Dr. Madow's in the Jefferson Hospital. I considered the blindness of hysterical origin while the patient was alive. I should like to ask Dr. Madow if he thinks there is a primitive subcortical visual capacity in human beings, such as is found in the lower animals. If this exists, it might account for this patient's capacity to perceive light and his vague form perception.

DR. J. RYAN: During the past summer I had the privilege of examining an 18-month-old child who, in my opinion, had cortical blindness. The diagnosis in the particular case was encephalitis of undetermined origin, and the child, although appearing moribund on several

occasions, eventually made a complete recovery. I had the privilege of seeing the child only recently, and there appeared to be no residuals. I would like to ask Dr. Madow if he would have been able to make a diagnosis of organic brain disease in his case without autopsy.

DR. AXEL K. OLSEN: Dr. Madow has well discussed the differential diagnosis of cortical blindness. What about some intracranial venous process as a possible cause of blindness? Would the EEG have been of help in making the diagnosis of organic cortical blindness?

DR. LEO MADOW: In answer to Dr. Yaskin's question: There was cerebral arteriosclerosis, which was probably chiefly responsible for the softenings. This man probably suffered from some degree of cerebral anoxia because of his pulmonary pathology. Basilar artery thrombosis is usually an insufficient cause of cortical blindness, because of the collateral circulation to the occipital lobes from the posterior communicating artery. In addition, in basilar artery thrombosis, one usually sees symptoms of brain stem involvement. In animals irrevocable blindness results from experimental destruction of Area 17 bilaterally. I agree with Dr. Ryan that it is extremely difficult to make a clinical differentiation of hysterical and organic cortical blindness. Dr. Olsen's thought about cerebral venous occlusions as a cause for cortical blindness is a good one. I cannot answer the question whether the EEG would be of help in the clinical diagnosis. This test would bear further investigation in such cases.

Femoral Nerve Complications of Gynecologic Surgery. DR. N. W. WINKELMAN JR.

Although various peripheral nerve complications of surgery occur during anesthesia because of direct pressure at a point where a nerve lies on a bony prominence, actual complications referable to the femoral nerve secondary to the actual surgical procedure are rarely reported.

Four practically identical cases were reported. In each case a hysterectomy was performed. After coming out of gas-oxygen-ether anesthesia, each patient had a nearly complete loss of femoral nerve function. There was loss of extension at the knee, impairment of flexion at the hip, absence of the knee jerk, and loss of sensation of the anteromedial surface of the thigh and the medial aspect of the leg and foot. All four women started to improve after a week, and all showed 70% to 90% improvement after six months.

In each case there was no known reason for this neuropathy. The surgical procedures were without complications. The laterality of nerve involvement was independent of the side of pathology. The anatomy of the nerve was reviewed. The site of involvement was above the inguinal ligament and below the formation of the nerve after the second, third, and fourth lumbar portions joined in the psoas muscle. It was felt that the retraction, packing, and pulling for over an hour caused a pressure neuropathy of the femoral nerve, such as is rarely seen after delivery. It is also suggested, owing to its rarity, that this complication occurs when the course of the femoral nerve is anomalous.

DISCUSSION

DR. AXEL K. OLSEN: Were these patients strapped down with a tight band around their hips?

DR. J. C. YASKIN: I recently saw two cases of femoral nerve palsy from abdominal surgery. The cause was undoubtedly pressure by retractors on the nerve as it emerges from the iliopsoas muscle. I believe we would hear of more such cases if surgeons would report all the complications of surgery.

DR. ARTHUR B. KING: I have seen a number of femoral nerve palsies associated with obstetrical deliveries. The cause is obviously pressure. Surgeons and obstetricians either do not recognize these nerve complications or refuse to believe that they occur.

DR. N. W. WINKELMAN JR.: In answer to Dr. Olsen's question: I do not believe it is possible for a tight strap around the patient's hip to compress the femoral nerve in the manner described.

Back Pain Due to a Loose Lumbar Facet. DR. ARTHUR B. KING.

One of the causes of sudden severe low-back pain is the unattached facet. This derangement produces episodic attacks of excruciating discomfort, usually with sudden onset and equally rapid relief of symptoms. The clinical course of six patients was discussed. There was no clear-cut symptoms complex, and at times a detailed x-ray examination failed to disclose the loose facet. The prevalent theories concerning its etiology were briefly discussed. Simple excision of the loose facet has yielded very satisfactory results. A wide and thorough surgical exploration was urged for patients with severe attacks of back pain despite negative x-ray studies.

DISCUSSION

DR. R. A. GROFF: I want to congratulate Dr. King on his presentation. In my operative experience in herniations of the nucleus pulposus, I have never encountered facets in the lumbar area that were attached to the vertebra by fibrous tissue, and therefore loose. The reason for this may be that we operate upon patients who have pain radiating into the leg and do not operate upon patients for low-back pain only. We have seen the lamina on one side attached to the base of the spinous process medially and to the pedicle laterally by fibrous tissue—the so-called floating lamina. In our three patients, this anomaly was associated with a herniation of the nucleus pulposus.

Dr. King's observations should be studied further and be called to the attention of the orthopedic surgeon, for it may very well be one of the causes of low-back pain.

DR. J. C. YASKIN: As I gather from this presentation, there are no criteria by which we can even suspect the existence of a "loose facet" prior to exploration. It is evident that these "loose facets" give rise to backache and pain along the roots. I am in the habit of designating low-back pain as mechanical or nonmechanical. The so-called mechanical back pain does not occur with spinal cord tumors. I therefore feel that orthopedic consultations should be routine in cases of recurrent backache. I am now wondering whether some of our unsuccessful results in disc surgery are not due to these "loose facets." Perhaps a more detailed laminography would permit of a preoperative diagnosis. Moreover, if one is in doubt, it would seem to me that the procedure as suggested by Dr. King is justified, since it is not formidable.

DR. H. C. JOHNSON, Reading, Pa.: I have never looked for loose facets, but I am certain I should find this condition if I looked hard enough.

DR. M. MOORE: I would like to ask Dr. King if he has ever had any negative findings in his exploration for loose facets.

DR. AXEL K. OLSEN: Several days ago I found a loose facet at operation. The patient's myelogram showed a complete obstruction of the oil. A loose facet was discovered lying on the root.

DR. ARTHUR B. KING: I have not used laminography. We find the spot film of L5 very helpful. I have been disappointed in orthopedic surgeons, most of whom, I consider, know little of back mechanics. They fuse but do not look. In answer to Dr. Moore's question, five of our cases of loose facet were unsuspected prior to exploration. Two correct preoperative diagnoses were made.

Axel K. Olsen, *Presiding*

Regular Meeting, March 4, 1955

Cerebral Arteriovenous Angiomas. DR. AXEL K. OLSEN and DR. M. N. WOOD (by invitation).

Cerebral arteriovenous aneurysm, or angioma, is a congenital vascular anomaly consisting of an abnormal communication between an artery and a vein. The arteries most frequently involved, in the order of frequency, are the middle, anterior, and posterior cerebral arteries. The incidence of this anomaly has been reported as 0.5% to 1% of all intracranial tumors. It occurs most frequently in males and is usually, initially, manifested clinically in the second or third decade of life. The commonest initial manifestation in more than 50% of cases is a convulsive seizure, usually of the Jacksonian variety. Hemorrhage and/or hemiparesis makes up the remaining 50%. Unilateral headache and bruit are common signs. Diagnostic aids, such as spinal puncture, skull x-ray, electroencephalography, and air studies are of some help, but arteriography is the most reliable procedure for diagnosis. Therapy before arteriography was limited primarily to decompression, carotid ligation, and radiotherapy. In recent years, direct surgical attack has been attempted. It is our purpose to emphasize a more drastic consideration of the surgical attack and present our experiences with six such problems. In all but one case there was intracranial bleeding. Three patients bled fatally; of the three, one was admitted in extremis. We demonstrated her lesion and operated, but she was beyond hope. The other two bled and recovered. The lesion was demonstrated by arteriography, but because one aneurysm was considered inaccessible and the other involved the dominant hemisphere, both patients were discharged on medication, only to return within a year and die of massive hemorrhage. Three patients sur-

vived surgery after the diagnosis was made by arteriography. Two of these bled almost fatally, and a third did not bleed but had a history of unilateral headache for 30 years. All three surviving patients are getting along to date. In view of the rapidly fatal hemorrhage, we are of the opinion that these cases should be approached surgically after accurate localization by arteriography, especially now that facilities for controlled hypertension and massive blood replacement are available.

DISCUSSION

DR. F. C. GRANT: I want to compliment Dr. Olsen and Dr. Wood on these cases. They apparently salvaged the few that could be saved. The surgical management of the occipital pole case and the frontal pole case were especially impressive to me. I tend to be a little more cautious in my approach to these lesions. Hypotensive anesthesia seems to be very helpful. The patients that died were probably beyond saving. I would like to ask the authors what drug is used for hypotensive anesthesia.

DR. R. A. GROFF: I agree with the authors that each patient must be evaluated and treated individually. No general rule can be given for the treatment of an arteriovenous anomaly. The patient in their series who had the Sylvian fissure anomaly was certainly an inoperable problem as we understand this lesion. I well remember my first exposure of a massive arteriovenous anomaly of the right parieto-occipital lobe. The patient was a woman who had a history of left-sided Jacksonian seizures of several years' duration. A pneumoencephalogram showed a large defect in the parieto-occipital area, and the diagnosis of meningioma was entertained. At operation, nothing more than inspection of the mass of veins and arteries was done. The patient was followed for two years and continued to have her seizures. We have about 10 cases and have operated in only 2. One of the two operative cases was a surgical emergency, since the patient returned to the hospital eight or nine months after arteriography in a state of coma. At operation, there was not much hemorrhage but considerable edema of the brain. Bleeding was severe but was finally controlled. She died rather suddenly, about 16 hours after operation. If this anomaly is in a silent area of the brain, it seems that surgical treatment is indicated.

DR. WILLIAM H. WHITELEY III: I recently operated on two arteriovenous anomalies at the Veterans Administration Hospital. One lesion was small and easily resected. Its removal was followed by hemiplegia, which disappeared after a few months. The other lesion was huge and nonresectable, and all I could do was to clip the middle cerebral artery after a massive subarachnoid hemorrhage. The patient was hemiplegic but finally made about a 75% recovery.

DR. J. C. YASKIN: I would like to put on record two interesting cases. One is that of a girl who at the age of 12 had a spontaneous subarachnoid hemorrhage. She was seen by a competent internist, who made a diagnosis of blood disease, and she underwent a splenectomy. I saw her about five years after the splenectomy, with another spontaneous subarachnoid hemorrhage and left hemiparesis. Arteriography revealed an arteriovenous anomaly. I prevailed on my surgical friends not to interfere, and, to the best of my knowledge, now several years after the arteriography, she is in good health. The second case was that of a middle-aged woman who presented bilateral exophthalmos and a loud bruit over the entire skull. Detailed arteriography revealed communications over most of the arteriovenous channels. She underwent, I believe, necessary surgery and is now getting along fairly well with a postoperative hemiplegia. I believe that every patient should have the benefit of contrast medium studies, but I am not so sure every patient should be operated on.

DR. F. MURTAUGH JR.: Desperate problems call for desperate measures. All Dr. Olsen's patients were obviously desperately ill, and I feel that he is to be congratulated on his efforts to save these people. I agree that, with improved surgical techniques, hypotensive anesthesia, and readily available whole blood, we are in a much better position to tackle these lesions surgically than ever before. There should be no hesitation at all if the lesion is located in a favorable area, such as the frontal lobe, the temporal lobe, or even the occipital lobe. On the other hand, each of these problems should be considered separately and on its own merit. If the patient does not have a major neurological deficit, or is not in immediate danger of losing his life, I believe surgical intervention should be withheld if such a procedure would produce an intolerable neurological deficit. I recall one patient of Dr. Scott's who has been followed at Temple University Hospital since 1940. She has been in and out of the hospital with a number of subarachnoid hemorrhages, and she has a large angioma in the left cerebrum, in its midportion. She has had no neurological deficit and has had no seizures. Operation has not been done because

of the obvious deficit it would produce. A number of these patients have been given the benefit of x-ray therapy, but angiograms following this treatment show no significant difference in the appearance of the lesion.

DR. AXEL K. OLSEN: In answer to Dr. Grant's question: The drug used is trimethaphen (Arfonad). We like to bring the systolic blood pressure down to within 60 to 70 mm. We were unable to do this in the patient with the Sylvian fissure anomaly. Prior to our more aggressive approach to this problem of arteriovenous anomalies, most neurologists and neurosurgeons used symptomatic therapy and continued observation. We did not find this passive approach successful. I want to emphasize again that when autopsy is performed in the cases of ruptured aneurysm it is ofttimes very difficult to find any pathological tissue characteristic of anomalies. This was particularly true in our patient with the pineal gland lesion. Olivecrona and his group do not hesitate to operate on any of these anomalies.

Diagnosis and Surgical Treatment of Temporal Lobe Epilepsy. DR. WILLIAM H. WHITELEY III, DR. WINSLOW J. BORKOWSKI (by invitation), and DR. NATHAN S. SCHLEZINGER.

Ten cases of temporal lobe epilepsy were presented in which the patients had been submitted to surgery. Eight of the patients were men, and two were women. The ages of the patients ranged from 24 to 60 years. The age at onset of seizures varied from 4 to 50 years. Three of the patients had grand mal seizures, also, and the rest had psychomotor seizures. All the patients had at least weekly seizures, and many of them had seizures every day.

The diagnosis of psychomotor epilepsy was made from the history and was verified by sleep records, as discussed by Gibbs. Routine electroencephalography was of very little value in localization. Localization was definitely made by sleep recordings, with use chiefly of the monopolar technique.

In nine cases, 6 cm. of the affected temporal lobe was removed completely. In one case the epileptogenic area was removed. All but one case showed in the EEG absence of spikes from the temporal lobe after operation. Likewise, all but the one patient (resection of the epileptogenic area) showed improvement. Three patients now have been free of psychomotor epilepsy for five years. Others have been free up to one year. Only three patients are maintained on small doses of anticonvulsant drugs. The patient with resection of the epileptogenic area showed no improvement clinically or in the EEG. Temporal lobe amputation has been of value in 9 of the 10 cases.

DISCUSSION

DR. WILLIAM H. WHITELEY III: We have had a few more patients than the total number reported in our paper. At this time, we are reporting only those patients with psychomotor epilepsy who were treated by temporal lobe resection. We would like to emphasize that this is not a surgical panacea. Only three patients had pathological lesions demonstrated at surgery. These lesions were middle cerebral aneurysm, porencephalic cyst, and osteophytes projecting into the temporal lobe from the floor of the middle fossa. We have done generous resections of the temporal lobe in order to remove all possible epileptogenic foci. In three cases we used electrocorticography, but we found this procedure deceiving and not of practical value. Adequate exposure of the brain was obtained with thiopental (Pentothal) anesthesia, head-dependent position, and spinal drainage with polyethylene tubing. We believe that these cases demonstrate the efficacy of temporal lobectomy.

DR. S. F. GILPIN: Did I hear correctly that 88% of these cases show focal signs in one temporal lobe? One of the patients who showed a unilateral temporal lobe focus, under a sleep EEG at Jefferson Hospital in 1952, was recently studied at Temple University Hospital. We could not duplicate the previous results. How can this discrepancy be explained?

DR. C. RUPP: I wonder over what time interval the authors collected their cases? Was the diagnosis of psychomotor epilepsy made on the clinical or the electroencephalographic findings? I have the impression that we do not see many cases which fit the clinical criteria for the diagnosis of psychomotor epilepsy. I also wonder how often the authors see spike effects in the temporal lobes in patients who manifest only grand mal seizures.

DR. F. C. GRANT: I agree with Dr. Rupp. In the last 15 years we have not seen a dozen cases of psychomotor epilepsy. I believe we did a surgical resection in one case. Have the authors followed any of these cases for more than five years after surgery?

DR. NATHAN S. SCHLEZINGER: The EEG tracings speak for themselves. Only the special sleep records bring out these temporal lobe discharges. Some of these patients had frequent psychomotor seizures daily, or almost so. After successful surgery the seizures were eliminated or tremendously reduced in frequency. It is well known that psychomotor epilepsy is usually refractory to drugs. However, prior to surgery we still use intensive drug therapy. There will certainly be a substantial number of psychomotor cases helped by neurosurgery. Dr. Gilpin's question is a good one. I wish merely to reiterate that properly made sleep records will reveal these spikes. A routine EEG ordinarily will not help in the diagnosis of psychomotor epilepsy.

DR. S. A. ZERITSKY: I saw a patient who had a negative EEG record in 1952. The recording was recently repeated and was positive for psychomotor epilepsy. I would like to ask the authors how their cases are selected for surgery.

DR. WINSLOW J. BORKOWSKI: In our positive cases the diagnosis was made only by sleep records. Psychomotor epilepsy is not very rare. We see a 10% incidence in our Epilepsy Clinic. Of this number, 85% show the spike effects in the anterior temporal lobe. It is extremely important that one must obtain all phases of the sleep record to find cases of this. The arousal phase is especially important. In response to Dr. Zeritsky's question, we use all the known drugs at first. If the patient shows no response or becomes paranoid, and if we can demonstrate a definite EEG focus, then surgery follows. After operation we neurologists keep these patients on medication for at least six months, then gradually reduce the drugs. The neurosurgeons take the patients off the drugs immediately.

Inciting Factors in Convulsive Seizures. DR. RODNEY A. FARMER.

In this paper convulsions were considered as an inherent property of the organism, and as such there is dispute that epilepsy is a manifestation of heredity. Evidence was also presented that convulsive behavior can be a release phenomenon, due to an overaction of the subcortical gray matter in the equation between the inhibiting effect of the cortex and the activity of the subcortical areas. Clonic activity is regarded as a possible exaggeration of the tremor, and tonic activity of the rigidity, of basal ganglia disturbances.

The convulsive phenomena are regarded as purposeful in the economy of the energy of the organism and accomplish physiologic sedation by a discharge and externalization of pent-up energy and thus help to reestablish the physiologic and psychic equilibrium. The convulsion also has features of self-punitive and of orgastic expressions.

Numerous clinical examples were cited in which there were evident psychological triggers in the situation in which the seizure occurs. Although some seizures seem to be precipitated by emotional stimuli, there is no evidence to assume that emotional factors are etiologically responsible for seizures.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

EFFECT OF ANAESTHESIA ON THE ACETYLCHOLINE CONTENT OF BRAIN. J. CROSSLAND and A. J. MERRICK, J. Physiol. **125**:56, 1954.

The amount of acetylcholine which could be extracted from the brains of rabbits, mice, and rats increased as a result of anesthesia, no increase being observed during anesthetic induction.

The fractional increase in the acetylcholine concentration depended, within limits, on the depth of anesthesia attained, but was independent of its duration.

In young rats, the fractional increase was approximately constant for each of seven anesthetic agents studied. Adult rats, mice, and rabbits suffered a different fractional increase in their brain acetylcholine contents, though each anesthetic studied (ethyl chloride and Dial) had the same quantitative effect in any one species.

While the amount of acetylcholine in the brain of a normal adult was higher than in the young rat, this difference was not found in anesthetized animals of the age used in this investigation.

The distribution of acetylcholine among four divisions of the brains of normal and anesthetized rats was studied. All areas of the brain participated, though unequally, in the rise in acetylcholine content; the pattern of this increase was the same for pentobarbital sodium as for ether.

THOMAS, Philadelphia.

ELECTRICAL STIMULATION OF THE UNEXPOSED CEREBRAL CORTEX. T. GUALTIEROTTI and A. SPENCER PATERSON, J. Physiol. **125**:278, 1954.

During stimulation of the motor cortex of baboons through external electrodes, discrete contralateral movements appeared at a certain strength.

During stimulation through electrodes placed over the two ends of the motor area, there was contraction of the ipsilateral muscles of the face and neck when the current had reached 2-4 ma. (frequency 20/sec.). When the strength was increased, the upper part of the arm also became involved, but never the forearm. None of this took place if the anode was moved to the middle of the motor area. With the anode in either position, discrete contralateral movements appeared when the strength was further increased: The muscles involved were different according to the frequency of stimulation, and the threshold varied between 70 ma. at 20/sec. and 40 ma. at 150/sec. All the movements developed progressively up to a maximum. At just threshold or slightly above, the muscles relaxed slowly as stimulation continued. With stimuli at less than 10/sec. the movements followed the frequency of stimulation, but this did not happen at higher frequencies. Stimuli at over 50/sec. induced first a maximal contraction of the particular muscles, then a period of relaxation; finally, slow pendular movements began, increased in amplitude, and after 40 to 50 seconds spread to other muscles also if the stimulation was continued.

There was always a delay between the beginning of stimulation and the onset of peripheral effects, and also between the first contraction and the spread to other muscles. With threshold stimulation at 20/sec. the maximum delay was 24 seconds. This decreased rapidly as either the strength or the frequency or both were increased.

In consecutive periods of stimulation no deviation of response was ever observed, provided that there were intervals of at least two to three minutes between them. After shorter intervals extension instead of flexion, or contraction of different muscles, could occur during stimulation of the same site.

A detailed analysis of the movements showed that at first they involved one muscle only or one group of muscles, producing a movement in only one direction. Other contractions appeared, if at all, only after delays of some seconds.

Near the cathode the electrical response appeared as a discharge of fast potentials on top of a slow negative wave; a negative spike preceded these two electrical changes. In the motor area far from the cathode and in the premotor area discharges of fast potentials, of increasing

duration, only appeared. In the sensory area and in the contralateral motor area no response was ever recorded.

During repetitive stimulation temporal summation of the slow activity and synchronization of the fast activity were recorded.

The first muscular movement analyzed by film recording was observed when the slow negative wave had reached nearly two-thirds of its maximum value and the synchronization of the spikes was almost complete; the muscles involved were correlated only with the area from which the slow waves and synchronous potentials were recorded.

During stimulation with bitemporal electrodes at a frequency of 250/sec. and a strength between two and three times the cortical threshold, a transitory contraction of most of the muscular system took place, which disappeared after two to three seconds of stimulation.

The recorded potentials were found to be similar to those obtained on the exposed cortex and to resemble closely the synaptic potentials and action potentials recorded from the spinal ventral roots.

The first negative spike has been interpreted as the immediate response of dendrites and axons of the first layer of the cortex, while the slow negative wave and spikes are due to internuncials.

The tendency of the fast activity to synchronize was taken as a further similarity to the spinal cord.

Fast activity alone, recorded far from the cathode, was not thought to be an index of excitation of the motor centers in the area involved: In fact, this activity was not accompanied by peripheral signs of cortical excitation.

The delay between the beginning of stimulation and the first muscular contraction was caused by the building up of the action potentials in the appropriate part of the cortex.

THOMAS, Philadelphia.

Neuropathology

Necrosis of the Brain Following Roentgen Irradiation. G. W. DUGGER, J. G. STRATFORD, and J. BOUCHARD, Am. J. Roentgenol. **72**:953 (Dec.) 1954.

Dugger, Stratford, and Bouchard report the case of a man who was given radiation therapy for a skin cancer located above the left ear. The treatment cured the cancer, but 26 months after the irradiation the patient became confused and forgetful. Neurological examination and a ventriculogram both suggested the presence of a mass lesion located inferior and lateral to the temporal horn of the left lateral ventricle. This mass was removed surgically. Grossly it appeared to be a glioma. The patient was improved by the operation but still had some confusion, dysphasia, and minimal right hemiparesis.

Histological examination of the portion of the brain which was removed at operation showed no evidence of a tumor. Necrotic gray and white matter was present, but the necrosis was much severer in the white matter. The foci of necrosis usually surrounded a blood vessel. All the blood vessels in the specimen had undergone some alteration. Several vessels had walls which were made up of a wide band of hyaline material. Others showed dense cuffs of lymphocytes around the vessel walls. Many of the vessels were completely necrotic. Some neurones survived, but the cortical cytoarchitecture was destroyed. There were many viable astrocytes in the cortex, but in the white matter almost all of them were destroyed.

The patient had been treated with a total dose of 4800 r (measured in air) over a period of 10 days. The radiation was generated at 150 kvp, filtered with 0.5 mm. of copper and 0.5 mm. of aluminum, and administered through a 5 cm. portal at a 25 cm. distance. This irradiation constitutes a rather high dose to the underlying brain in a short period of time. However, it is not unusual to irradiate normal brain tissue with larger doses than this in treating pituitary adenomas. Usually the radiation is given over a considerably longer period of time, however. Radiation for brain tumor is usually administered in greater dosage than this patient received.

Dugger, Stratford, and Bouchard feel that the abnormality in the brain in this case was focal degeneration and necrosis secondary to vascular occlusion from periarteritis and endarteritis. The necrosis was probably caused by the radiation, which had been administered in relatively high intensity in a short period of time. The degeneration was greater in the white matter than in the cortex, probably because the cortex has a more abundant blood supply, which is not compromised as quickly as the blood supply of the white matter. The area of necrosis in the brain imitated a tumor in symptoms, neurological signs, ventriculographic findings, and gross appearance.

WEILAND, Grove City, Pa.

The Phosphatases of the Nervous System. I. FEIGIN and A. WOLF, J. Neuropath. & Exper. Neurol. **14**:11 (Jan.) 1955.

Feigin and Wolf discuss the phosphatases, a group of enzymes which catalyze the liberation of inorganic phosphate from phosphate esters, and certain general principles regarding enzymes and histochemical studies concerned with these agents. They note that the effect observed is the summation of many influences (enzymes, coenzymes, activators, inhibitors, concentration, and substrates), that these influences are often difficult to measure separately, and that it is more convenient to speak in terms of the "enzyme activity" noted in a given situation. Histochemical preparations for demonstrating enzyme activity cannot be treated in the sense of a special stain, for it is not the enzyme itself which is being demonstrated, but, rather, the effect of enzyme action, and this may be complex. Several enzymes may split the same substrate, so that a single preparation may demonstrate the effect of two different enzymes, the delineation of which may be difficult. Thus, the observed histochemical pattern with a single substrate may be the result of a complex of enzymes rather than a single enzyme. Artifacts of varied nature have to be contended with, and certain of these are discussed. Difficulties in enzyme location may also result from diffusion of the enzyme.

The present classification of enzymes of the phosphatase group must be considered tentative and partial. Data concerning the distribution of various phosphatases in tissues of the nervous system are reviewed, as well as some of the methods used for demonstrating these several enzymes. One of the most carefully studied groups of phosphatases is alkaline phosphomonoesterase, and there is evidence of its activity in the endothelium of blood vessels, the choroid plexus, the arachnoid cells, and, diffusely, the neural parenchyma, being more marked in the gray than in the white matter. The area postrema has been reported as highly active. The hypothalamic nucleus in the rat has been reported as being active. Alkaline phosphatase has been demonstrated histochemically in the cells of the meningioma, in the cell processes of astrocytes in astrocytomas, and in glioblastomas. The plaques of multiple sclerosis have been described as indicating increased alkaline phosphatase activity.

Acid phosphomonoesterases form a group which is most active at a pH of about 5. Preparations for this enzyme revealed staining of neurons, particularly the larger neurons and those in the brain stem and spinal cord. The nucleus is reported as being both stained and unstained. Neurofibrillar staining has been specifically reported. Activity was increased in the cell bodies of neurons undergoing central chromatolysis and in the glial tissues about degenerating fiber tracts.

Briefer comment and distribution patterns are reviewed on 5-nucleotidase, phosphamidase, pyrophosphatases, adenosinetriphosphatase, phosphoacylases, and nuclear phosphomonoesterases.

SIEKERT, Rochester, Minn.

Diseases of the Brain

NEUROLOGICAL ASPECTS OF INDUSTRIAL MANGANESE POISONING. J. BOYER and J. RODIER, Rev. neurol. **90**:13, 1954.

Twenty-one cases of chronic manganese poisoning among miners have been detected in two years. These workers are most susceptible because they are compelled to breathe for long periods the dust stirred up by their tools. Three cases are reported. The first is that of a 20-year-old man who, after working in a mine for five years, complained of pains in his knees and neck and exhibited involuntary laughing, fixed facies, fine tremors, cogwheel rigidity, adiadokokinesis, and difficulty in walking backward. The second patient, after eight months of exposure, began to experience chest pains, had a febrile episode for eight days, and then began to experience cramping pains, paresthesias, and weakness of the extremities. His gait was so impaired that he had difficulty in descending an incline or walking backward. There developed somnolence, psychomotor retardation, and periods of excitement. Bulbar symptoms were evident in the fixed facies, slowing of speech, stammering, and difficulty in opening the mouth. There was hypesthesia of the extremities and weakness of the hands and feet. Adiadokokinesis, dysmetria, Rombergism, and severe ataxic gait were observed. There also developed a fixed deformity of the hands and a skipping type of walking on the toes, called a rooster step, "*pas decoq.*" Ultimately the weakness and contractures of the hands and feet made the patient bedridden. Manganese was found in the hair, feces, and bile. The third subject had been a miner for six months when he began to complain of headaches, weakness, and somnolence. There developed a bulbar syndrome, con-

sisting of immobile facies, dysphagia, and dysarthria. There was weakness of all extremities and a marked ataxia, so that he seemed to run after taking a few steps. There was also a marked psychological disturbance in the form of euphoria and inappropriate affect. Manganese was found in the hair, nails, and feces.

BERLIN, New York.

RECURRENT OCULOMOTOR NERVE PARALYSIS SECONDARY TO PITUITARY TUMOR. C. MOROCUTTI and L. TRAMER, Acta neurol. **8**:1020 (Dec.) 1953.

Morocutti and Tramer report the case of a 25-year-old woman, hospitalized for severe episodes of right-sided headaches, of four months' duration associated with transient ptosis on the right and with lasting weakness of the right lateral rectus. The past history was positive only for oligomenorrhea of six years' standing. Neurologic examination revealed ptosis, internal and external third nerve ophthalmoplegia, and weakness of the fourth and sixth nerves on the right. The spinal fluid was under normal pressure but showed a slight elevation in protein. Skull films were not considered remarkable. The EEG revealed diffuse abnormalities on the right. Percutaneous and open angiography demonstrated occlusion of the right internal carotid artery at the upper level of the siphon. During the patient's hospitalization, the ocular findings fluctuated, with exacerbations occurring premenstrually, in association with severe headaches. Death followed the rapid development of right trigeminal involvement, stiff neck, and coma. Autopsy demonstrated the presence of an encapsulated neoplasm which occupied the sella turcica, eroding into the sphenoid bone and compressing the right carotid artery against the cavernous sinus. The histologic report was chromophobe adenoma with multiple areas of hemorrhage and necrosis. The periodic exacerbations of the ocular signs are considered to result from direct pressure secondary to hemorrhages within, and edema of, the tumor.

NORSA, New York.

Treatment, Neurosurgery

THE LONG TERM EVALUATION OF PREFRONTAL LOBOTOMY IN CHRONIC PSYCHOTICS. R. F. MEDINA, J. S. PEARSON, and H. F. BUCHSTEIN, J. Nerv. & Ment. Dis. **119**:22 (Jan.) 1954.

Forty-six chronic psychotic patients subjected to lobotomy in 1941 and 1942 were reevaluated eight to nine years after the operation, and they were compared with a control group not so treated but otherwise similar. The behavioral status of the two groups was evaluated by psychiatrists, a psychologist, a social worker, and the nursing and attendant staff. The rating scale was based on the extent to which the patient had regained his effectiveness in living and dealing with other persons. Extensive psychologic tests were administered. The mean rating score of the lobotomized group was that of improvement, but the control group was unchanged. Forty-seven per cent of the surgical group showed "complete recovery" or "marked improvement," but only one subject in the control group showed "marked improvement." Only 8% of the surgical group remained unchanged or became worse, but 88% of the control group remained unchanged or became worse. There was no significant difference in degree of improvement between the lobotomized subjects who developed seizures and those who were seizure-free. The findings did indicate that the longer the duration of the psychosis, the less the degree of permanent improvement. Of the 20 patients who reached peak adjustment levels, 25% reached their optimal adjustment within one year after operation and 60% within five years, but 40% continued to improve up to eight years after the operation. A number of lobotomized subjects slipped back after reaching a peak, but never to the preoperative level. Psychological tests indicated an impairment in the ability to comprehend a total situation and to plan ahead.

BERLIN, New York.

PROGRESSIVE EXOPHTHALMOS FOLLOWING THYROIDECTOMY CURED BY IRRADIATION OF THE CEREBRAL CENTERS. A. T. BERKMAN, Radiology **62**:406 (March) 1954.

Berkman reports on a patient with exophthalmos and symptoms of hyperthyroidism, both of which were relieved by deep x-ray therapy to the pituitary gland. The patient's first symptoms had been anorexia, weight loss, abdominal pain, diarrhea, rapid pulse, and protrusion of the eyes. He was treated by iodine medication for one year, but during that time his symptoms became worse and his basal metabolic rate progressed from +28% to +58%. Both lobes of the thyroid gland were enlarged and tender. A thyroidectomy was performed in May, 1949. Some of the symptoms were relieved by the operation, but the exophthalmos became worse. Before the x-ray

therapy was given in 1951, the patient had a severe tremor, a rapid pulse rate, insomnia, abdominal pain, and diarrhea. Berkman treated the area of the pituitary gland through three skull portals, giving a dose (presumably the air dose) of 800 r per portal in 49 days. The exophthalmos was markedly improved by the therapy. All symptoms of hyperthyroidism were considerably improved also.

The author points out that treatment of the thyroid gland itself in hyperthyroidism with the associated exophthalmos often fails to correct the exophthalmos. He feels that the logical approach to the problem is irradiation of the pituitary gland. WEILAND, Grove City, Pa.

TREATMENT OF TRIGEMINAL NEURALGIA WITH VITAMIN B_{12}. S. J. SURTEES and R. R. HUGHES, Lancet **1**:439 (Feb. 27) 1954.

Surtees and Hughes treated 18 cases of trigeminal neuralgia and 1 case of glossopharyngeal neuralgia with vitamin B_{12} intramuscularly, giving an initial course of 1000γ daily for 10 days, followed by 1000γ twice weekly for five doses. Some patients received 1000γ twice daily for periods up to three weeks without any apparent harm. The results of treatment were as follows: little or no immediate improvement in 3 cases; moderate improvement in 1 case, and considerable improvement or complete relief of pain in 15 cases (80%). Of the three cases with no improvement, one received only a small dose of vitamin B_{12}, and a second had only mild to moderate pain before treatment and it was very difficult to estimate the results.

In some cases the neuralgia subsided only slowly during treatment; in most of those cases in which improvement took place, it was quite sudden and was noted after the second or third injection. The authors conclude that vitamin B_{12} can produce a remission which may be continued for a long time but there is no evidence that this is a cure, and maintenance therapy may be required. MADOW, Philadelphia.

EFFECT OF CHLORPROMAZINE (LARGACTIL—4560 RP) ON PARKINSONIAN SYNDROMES. A. BALESTRIERI and M. MONTANARI, Rass. neurol. veget. **10**:395 (Oct.) 1953.

Fifteen men and women with either postinfectious or idiopathic Parkinsonism of 4 to 35 years' duration and ranging in age from 44 to 63 years comprise the present series. They were given chlorpromazine intramuscularly or orally daily over a period of one month (25-50 mg. i. m.; 50-100 mg. p. o.). Variable effects on both tremor and rigidity were noted, with improvement in some cases, no change in others, and worsening in some. A mild drop in blood pressure and drowsiness were the only side-effects observed. EEG's done on two patients showed no alteration following the administration of the drug. The authors feel that, while chlorpromazine is of no particular value in the treatment of Parkinson's disease, the improvement noted in some of their patients justifies further trials with chemically related compounds. NORSA, New York.

Encephalography, Ventriculography and Roentgenography

ROENTGEN DEMONSTRATION OF CERVICAL NERVE ROOT AVULSION. J. E. WHITELEATHER, Am. J. Roentgenol. **72**:1017 (Dec.) 1954.

Whiteleather reports a series of eight cases in which the diagnosis of cervical nerve root avulsion was made as a result of the history, physical findings, and cervical myelogram. Two of the eight patients had surgical exploration, and the diagnosis was verified in each case, although no reconstruction of the nerves involved could be performed in either patient in which exploration was done. Avulsion of the cervical nerve roots occurs as a result of an injury which forces the shoulder downward while the head either is held fixed or is pushed in the opposite direction. If the roots are avulsed within the neural foramen, the injury is thought to be irreparable. However, if the avulsion occurs outside the neural foramen, there is some hope that a repair might be successfully performed. In the series of cases which Whiteleather reports, the shortest interval between the injury and the myelogram study was 3 weeks, and the longest interval was 15 years.

There are two roentgenographic findings which Whiteleather believes enables one to make a diagnosis of avulsion of the cervical nerve roots in persons who have had an injury to produce such avulsion and who have clinical symptoms compatible with the diagnosis. The first finding is the demonstration of one or more extradural collections of the opaque oil in pockets lying in

or alongside the intervertebral neural foramina. The opaque oil enters these pockets through a tear in the dura which has been left by the avulsed root. The second finding is absence of a normal root shadow and a smooth, straight contour or a tiny notch where the normal root shadow should be. The latter sign is found when the dura has healed over the site of avulsion.

WEILAND, Grove City, Pa.

DISSOLUTION OF THE INTERVERTEBRAL DISK IN THE AGED NORMAL. J. GERSHON-COHEN, H. SCHRAER, D. M. SKLAROFF, and N. BLUMBERG, Radiology **62**:383 (March) 1954.

Gershon-Cohen and his associates performed roentgenologic bone survey examinations on residents of a home for the aged. The subjects were healthy enough to be ambulatory and had no disabling complaints or complaints requiring medical attention associated with the skeletal system. Anteroposterior and lateral roentgenograms of the dorsal and lumbar spine were obtained on 130 of these people. Eighty-two were women, and 48 were men.

Gershon-Cohen's report is concerned with 27 cases from this group of normal old people in which the vacuum phenomenon was observed in the roentgenograms of the spine. He uses the term "phantom nucleus pulposus" to describe the vacuum phenomenon as seen in the intervertebral disc space in roentgenograms of the spine. Twenty of the 27 patients whose films presented the phantom-nucleus finding had never had any complaints referable to the spine. The orthopedic studies showed no greater incidence of immobility of the spine in those who exhibited phantom nuclei than in those who did not. In 8 cases the phantom nucleus was limited to one interspace; in 19 the finding was multiple. The commonest interspaces involved were the low dorsal, the first lumbar, and the fourth and fifth lumbar. In one patient six interspaces were involved. Minimal or moderately advanced hypertrophic degenerative changes were found in practically all cases. Narrowing was the rule in interspaces involved by the phantom-nucleus phenomenon. Spondylolisthesis was associated with the phantom nuclei in eight cases, and in six of these cases the upper vertebral body was displaced posteriorly rather than anteriorly.

The vacuum phenomenon is thought to be caused by drying out of the substance of the nucleus pulposus. The diminution in body stature in the aged can be explained, in part, by drying and thinning of the intervertebral cartilages.

WEILAND, Grove City, Pa.

A SOURCE OF POTENTIAL ERROR IN THE ROENTGEN DIAGNOSIS OF CERVICAL RIBS. D. R. KEATING and J. R. AMBERG, Radiology **62**:688 (May) 1954.

A costal and a transverse process develop from each side of the seventh cervical vertebra in children. The rate of growth of one is independent of the rate of growth of the other. Either process may be the longer. The ends of the two processes normally fuse between the 4th and 10th year of life, leaving a foramen, the costotransverse foramen, between the vertebral body and the fused ends of the processes. A long costal process, before fusion occurs with the transverse process, can sometimes be misinterpreted as a cervical rib in roentgenograms of children. Other sources of possible error in diagnosis are anomalous development of one or both first thoracic ribs and the possible presence of 13 pairs of ribs.

Keating and Amberg believe that when cervical ribs are present they are ossified and identifiable at birth, since they are formed in the same manner as the normal ribs. During growth they maintain their original size relationship with the other ribs. Keating and Amberg have found no newborn infants with cervical ribs, but they have observed them in children 6 weeks of age and older.

WEILAND, Grove City, Pa.

MYELOGRAPHY IN SPINAL METASTASES. S. HEISER and A. J. SWYER, Radiology **62**:695 (May) 1954.

Heiser and Swyer performed myelograms on 75 patients with tumors of the spinal canal; 20 had metastatic cancer and 6 had lymphoma. The incidence of 26 cases with these malignant diseases out of a total of 75 cases of tumors of the spinal canal is high. Heiser and Swyer explain this high incidence by the fact that the institution in which the work was done (Montefiore Hospital, in New York) has a large tumor service.

The presenting symptoms and signs of epidural tumors are usually those of nerve root compression. In 12 of the 20 cases of metastatic cancer plain films of the spine showed evidence of bony metastasis. In 10 of the 12 cases the evidence of bony metastasis coincided with the level of cord compression which had been determined clinically. Roentgenograms of the spines of the

six patients with epidural lymphoma masses showed no evidence of involvement of the bones. Measurement of the interpediculate space is not usually helpful in the case of cancer metastasis or lymphoma. It is the slow-growing tumors, such as neurinomas or ependymomas, which cause erosion or displacement of the cortex of the bone.

Myelograms proved helpful in the diagnosis of the reported tumors. Positive myelographic findings usually consisted of complete block of the opaque column, partial block, or pressure defects on the opaque column. The differential diagnosis must include any intramedullary, intradural, or epidural mass which could produce such a finding. Heiser and Swyer believe that the intramedullary tumors are easily differentiated because their configuration in the myelogram films is characteristic. Intradural, extramedullary tumors are more difficult to differentiate from the epidural tumors. Characteristically they are more sharply demarcated, but may fail to give the characteristic appearance. In general, one would have to admit that the defects found in myelograms of patients with epidural metastasis or lymphoma are not specific but that they can substantiate the clinical impression of a mass causing pressure on a nerve root. Early laminectomy under such circumstances is usually indicated. WEILAND, Grove City, Pa.

CALCIFICATION OF THE INTERVERTEBRAL DISKS IN CHILDHOOD. F. N. SILVERMAN, Radiology **62**:801 (June) 1954.

Calcification may occur in the nucleus pulposus or in the annulus fibrosus or in both. It occurs also in the cartilaginous plates of the vertebral bodies, but this type has not been observed in children. Calcification in the annulus fibrosus is much commoner at all ages than calcification in the nucleus pulposus, and probably represents a degenerative change which is usually of little or no clinical significance. Alkaptonuric ochronosis can produce a generalized calcification of both the nucleus pulposus and the annulus fibrosus of many intervertebral discs. The deposits of homogentisic acid in the cartilage ultimately cause degeneration of the cartilage, with clinical and roentgenologic manifestations of arthritis in addition to the calcification.

A third type of calcification occurs in the nucleus pulposus only. Its cause, whether or not it produces or is accompanied by symptoms, and its permanence are unsettled problems. Weens has described a calcification of the nucleus pulposus which occurs in childhood, is associated with clinical symptoms, and is of a transient nature. Other authors have demonstrated obvious calcification of the nucleus pulposus in children which has later disappeared. The suggestion has been made that those cases in which calcification is present and is apparently accompanied by acute symptoms, such as pain and stiffness in the region of the spine involved, and in which the calcification later disappears are very similar to the disease variously known as peritendinitis calcarea, myotendinitis calcarea, or "bursitis." However, there are also asymptomatic calcifications of an occasional nucleus pulposus in children, some of which disappear and some of which remain for long periods of time.

Silverman reports case histories of seven children, varying in age from 5 months to 11 years, in whom calcifications of the nucleus pulposus were demonstrated roentgenologically. The finding was thought to be an incidental observation in five of the seven patients and was associated with symptoms in the region of the calcification in two. WEILAND, Grove City, Pa.

CONGENITAL ABSENCE OF THE ODONTOID PROCESS. T. M. FULLENLOVE, Radiology **63**:72 (July) 1954.

Fullenlove describes a case in which a patient had sustained some trauma to the head, followed by pain in the neck and in the left trapezius muscle. The pain occasioned an x-ray of the cervical spine. This x-ray showed that no odontoid process was present. The upper margin of the second cervical vertebra was flattened. This is the ninth case of this anomaly recorded in the medical literature since 1933. WEILAND, Grove City, Pa.

Books

Fundamentals of Psychoanalytic Technique. By Trygve Braatøy. Price, $6.00. Pp. 404. John Wiley & Sons, 440 4th Ave., New York 16, 1954.

The author, now deceased, was a Norwegian psychoanalyst of considerable experience and erudition. While working in this country he devoted considerable time to writing this genuinely fascinating book. It is filled with the author's subjective judgment of others' work and writings in the form of pertinent extracts along with results of his own experiences. These statements make the reader feel a sort of teacher-student relationship with the author. They also remove the book from the category of a dry text. The writing is superbly informal and maintains the reader's attention. The contents are excellently informative. There is an adequate bibliography and index. This excellent book is highly recommended.

Fundamentals of Neuropathology. By William B. Dublin. Price, $18.50. Pp. 685 + XXIII, with 329 figures. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1954.

The author's resolution to reunite the pathology of the nervous system and that of the remainder of the body is commendable; it is one of many indications of the general trend in the neurological field. Some neuropathologists, to say nothing of neurologists, have become highly specialized by reason of falling into ignorance of all else, which, as Clifford Allbutt noted long ago, is vain pretension. Neuropathologists have very nearly had their own private means of communication and special staining techniques, and the latter, while they undoubtedly have been important adjuncts, have been in the way of becoming the tail that wagged the dog. Dublin has attempted to redress these incongruities with straightforward description in plain English and with the use of relatively simple histologic method. His direct statements in some instances will likely be considered dogmatic.

The author, formerly of the Indianapolis General Hospital, is the Chief of Laboratory Service at the Veterans Administration Hospital, Denver, and an associate professor of pathology at the University of Colorado School of Medicine. His book is indicative of a wide practical experience, and it might well serve as a useful reference to a hospital department of pathology. Its massiveness may perhaps have the advantage of discouraging its being made off with; the 70-pound glossy paper may be responsible for its burdensome weight. It is unlikely that the undergraduate student or physician will be frustrated on consulting this book, since he will find something interesting and useful about the topic with which he is concerned. The illustrations are many and are generally good; in a few there is formaldehyde "wrinkling," where a brain has been sectioned before fixation. There are just enough clinical data in the descriptions of the "fundamentals" to spice the topic properly for those interested, but not too much to discourage the nonclinician.

In reviewing a treatise of this size, it is tempting to ride hobbyhorses. In this regard, my personal wish would be that the references, which comprise 496 items, occupying 26 pages, should be alphabetically arranged to enable one to find certain works quickly. Moreover, it would seem unlikely that the British and Continentals have been as unoccupied in neuropathology as their infrequent appearance among these references would appear to indicate. However, it should be noted that the author has made a deliberate attempt to confine his references to those readily available.

Among rare omissions, I could find no discussion of an increasingly recognized cause for lesions in the brain, namely, thrombosis of the internal carotid artery. Also, a description of the effects of spinal anesthesia on the central nervous system was not found; the late Foster Kennedy indicated his concern about them when he said that if spinal anesthesia were the only form available and he required an amputation of the leg, he would find a surgeon who operated with dispatch, gulp down a pint or so of whisky, and tell him to go ahead.

Some will be bound to compare in an unfavorable light the pages devoted to one or another topic, depending on their particular interests. I believe neoplasms of the nervous system do not require some 23% of space in a book devoted to fundamentals of neuropathology. Despite these

personal preferences, Dublin's book is soundly conceived and well executed. What is most important, it does not disappoint the reader, and for anyone in need of an interesting and reliable reference, these "Fundamentals of Neuropathology" can be recommended.

1955 Medical Progress. By Morris Fishbein, M.D. Price, $5.00. Pp. 346. Blakiston Division, McGraw-Hill Book Company, Inc., 1955, 575 Madison Ave., New York 22.

This is the third issue of "Medical Progress." In this book, Morris Fishbein, the capable editor, has outlined the growth and advances in all the medical and surgical specialties during the past year. He has done this with the help of prominent specialists from the most noted teaching institutions in the country.

Almost every field of medicine has shown remarkable advances during the past year. As in the past few years, much of this had to do with the introduction of still newer antibiotics and new drugs. Perhaps most startling is the appearance of chlorpromazine, which is now used in many different areas. Not only is it useful in anesthesia and for the lowering of body temperature, but it has shown remarkable possibilities in a variety of mental diseases. It seems that drugs of this type tend to modify the metabolism of brain tissue, and their use will have most noteworthy effects. In the field of x-rays, medicine has benefited by the use of new contrast media. The use of adrenal cortical steroids as therapeutic agents for various diseases, including rheumatoid arthritis, now seems stable and well established. In the field of dermatology the use of hydrocortisone during the past year has proved that in ointment form it is a valuable addition to the dermatological armamentarium.

Of unusual interest is the changing attitude of researchers in regard to the anatomy of the liver. The concept of Hans Elias that the liver consists of an irregular mass of epithelial cells tunneled into by blood capillaries is now slowly taking the place of the concept of liver-cell cords. This changing in anatomic concept helps us to understand certain phases of liver injury.

The chapter on the ear, nose, and throat seems to be the only one written in the stilted style of the old A. M. A. *Journal*. The review of medicine, by Morris Fishbein, is written in the usual efficient way that only Morris Fishbein is capable of.

For the general practitioner this book seems to serve in much the same way that the annual "Year Books" serve the specialists. The book is well printed on good quality paper. Each chapter has adequate references, and the book is well indexed and well bound. In a nutshell, this is a good compend of recent medical progress.

Psycho-chirurgie et fonctions mentales. Techniques—résultats applications thérapeutiques. By Jacques LeBeau. Price, not given. Pp. 429, with 78 illustrations. Masson & Cie, 120 Boulevard Saint-Germain, Paris, 1954.

LeBeau has gathered together his observations over the past several years on 175 patients treated by psychosurgery, principally topectomy. His choice of material has been fortunate, since the majority of patients have been of the type that could cooperate in the preoperative and postoperative studies. A considerable section is devoted to the psychologic study along the lines devised by Eysenck and applied by Petrie. The author presents the varied techniques of leucotomy, topectomy, cortical undercutting, etc., and furnishes detailed descriptions of his personal surgical methods. He stresses the importance not only of adequate exposure of the operative field, so that incisions and excisions can be done under direct vision, but also of recording the location of the incisions by means of roentgenologic verification with a variety of contrast mediums. Only in this way can the surgeon reach valid conclusions concerning the location and extent of his operations.

The over-all surgical mortality of 5.5% is somewhat disquieting, but is prominent, particularly in patients operated upon for the relief of pain. Older patients withstand these extensive operations with some difficulty. Postoperative epilepsy has been less than 5%, however, in patients who did not have convulsions before operation. Other complications have been unimportant: particularly evident is the absence of infections, indicating excellent toilet of the wounds and liberal use of antibiotics.

The results of topectomy in schizophrenia are 30% satisfactory and 40% failure, thus indicating that the operations are equally successful with lobotomies. On the other hand, the good results in the depressions and psychoneuroses are at least double. Furthermore, there is a notable absence in topectomized patients of the severe frontal lobe syndromes that often follow major lobotomy. LeBeau has attempted selective operations in a wide variety of neurotic and psychotic

patients and from his observations and psychologic tests has erected a number of clinical syndromes following one or another of the topectomies. The personality alterations following operations in the various areas of the frontal lobes give some indication of the type of operation to be employed when one is faced with certain clinical syndromes. Seven syndromes are distinguished: Resection of the dorsal convexity gives rise to a mixture of affective indifference and restlessness, with euphoria. The syndrome of the rostral convexity is of the same type, but less marked, consisting mostly of affective indifference, with freedom from anxiety. Resection of the orbital surface gives rise to considerable inertia, with marked reaction to physical and psychologic stimuli. Euphoria is present, but without the excitement seen with superior cuts. There is no confusion, but there is asthenia rather than inertia. Posterior orbital operations cause considerable inertia, so that patients have to be fed. Cingulectomy produces a decided calming effect, with less irritability and no agitation. The patients are lucid, talk normally, and present no disorientation or confusion. Relaxation and friendliness are noted by the ward personnel. The syndrome of the frontal pole is not clear-cut, perhaps because of complications occurring in a number of patients. Euphoria, with mixtures of excitement and indifference, seems to be especially characteristic. The syndrome of the internal surface of the frontal lobes is also not clear-cut, since symptoms appear significantly only when the base is involved (inertia) or when the convexity is included (hypomania). Resection of the lateral aspect of the frontal lobes was done only in four patients, mostly with advanced malignant disease. Confusion and disorientation were particularly notable, and, according to the author, are like those observed in major lobotomy.

From the psychologic standpoint, selective operations are aimed at various psychologic deviations, such as may be isolated by the Eysenck tests. To begin with, there is no lowering of the intellectual scores following selective operations, such as is said to follow lobotomy. Operations on the convexity reduce neuroticism and introversion, while they leave psychoticism relatively unchanged. Cingulectomy diminishes neuroticism and psychoticism, while leaving unchanged the balance between extroversion and introversion. Section of the internal surface gives rise to rather intermediate results. Distractibility is increased after lobotomy, but reduced after orbital operations, and more so after cingulecomy.

LeBeau concludes that the effects of operations on the frontal lobes cannot be explained on the basis of a quantitative difference only. Although there is a more marked effect from extensive operations than from restricted ones, there is enough evidence to show that different functions are involved when different areas of the frontal lobes are resected. Discussing the mode of action of frontal lobe operations, the author stresses the compensatory processes. "In a general way, we believe at the present time that the most satisfactory explanation of the therapeutic action of psychosurgery is the compensation, the equilibration, the normalization that is brought about by selective frontal operations."

This volume covers a great deal of territory. Topectomy has been applied in a large variety of conditions, ranging from uncontrollable pain with normal psyche to mental deficiency with epilepsy. The variety of operations applied reduces the number in any one category to rather small proportions. The possibility of involvement of additional areas due to venous or arterial destruction, "parasurgical necrosis," and postoperative brain swelling has not been adequately considered. Anatomical controls, with studies of distant degenerations, will take years to accomplish. Recent reports of relapses after selective operations on the frontal lobes in other clinics should sound a note of caution, particularly since the follow-up period in LeBeau's cases is seldom over three years, and it is known that relapse may occur after excellent postoperative adjustment for as long as ten years. The most significant therapeutic results reported in this monograph have to do with the relief of personality defects in patients with epilepsy by means of cingulectomy. There is also a beautiful color plate showing extraordinary reduction in the shiny swelling of causalgia within a day after resection of the convexity. The effects of the various topectomies on neurotic and psychotic disorders do not differ markedly from those obtained with other psychosurgical procedures.

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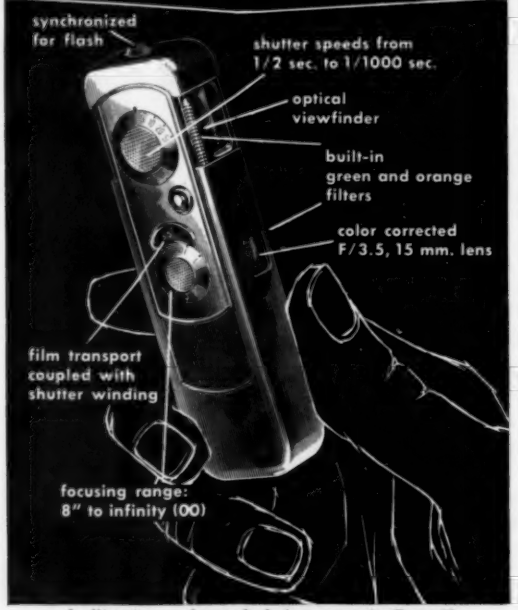
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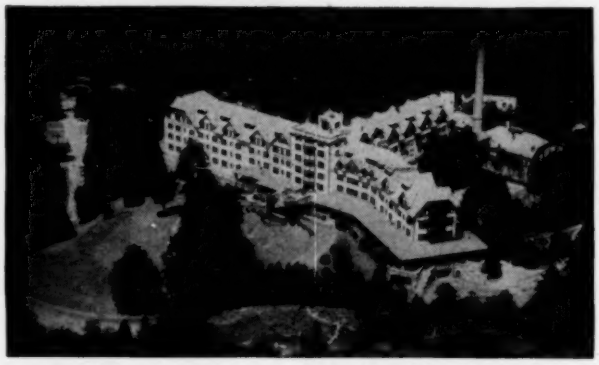

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